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CONTENTS

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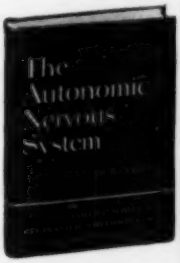

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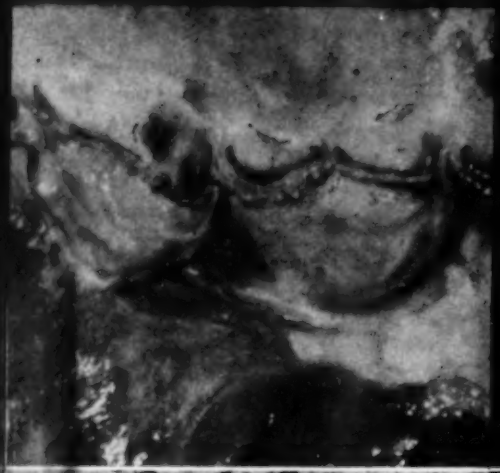
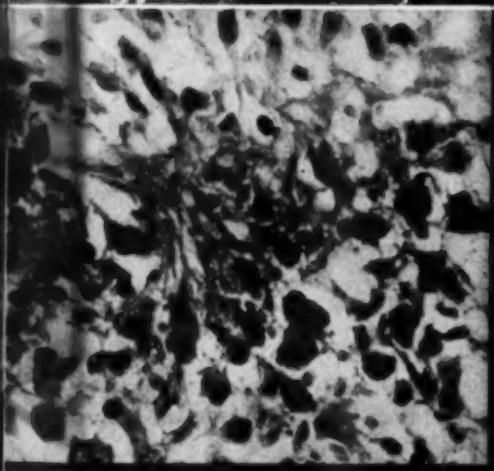


q. Does cortisone influence the heart lesions of rheumatic fever?

a. Early cortisone administration suppresses and in some cases may even prevent serious cardiac damage.



q. What effect does cortisone have on acute rheumatic fever?

a. Often within 24 hours after cortisone therapy, the severely ill, toxic patient appears alert and comfortable; and within one to four days, temperature drops to normal, appetite increases, and polyarthritis subsides.

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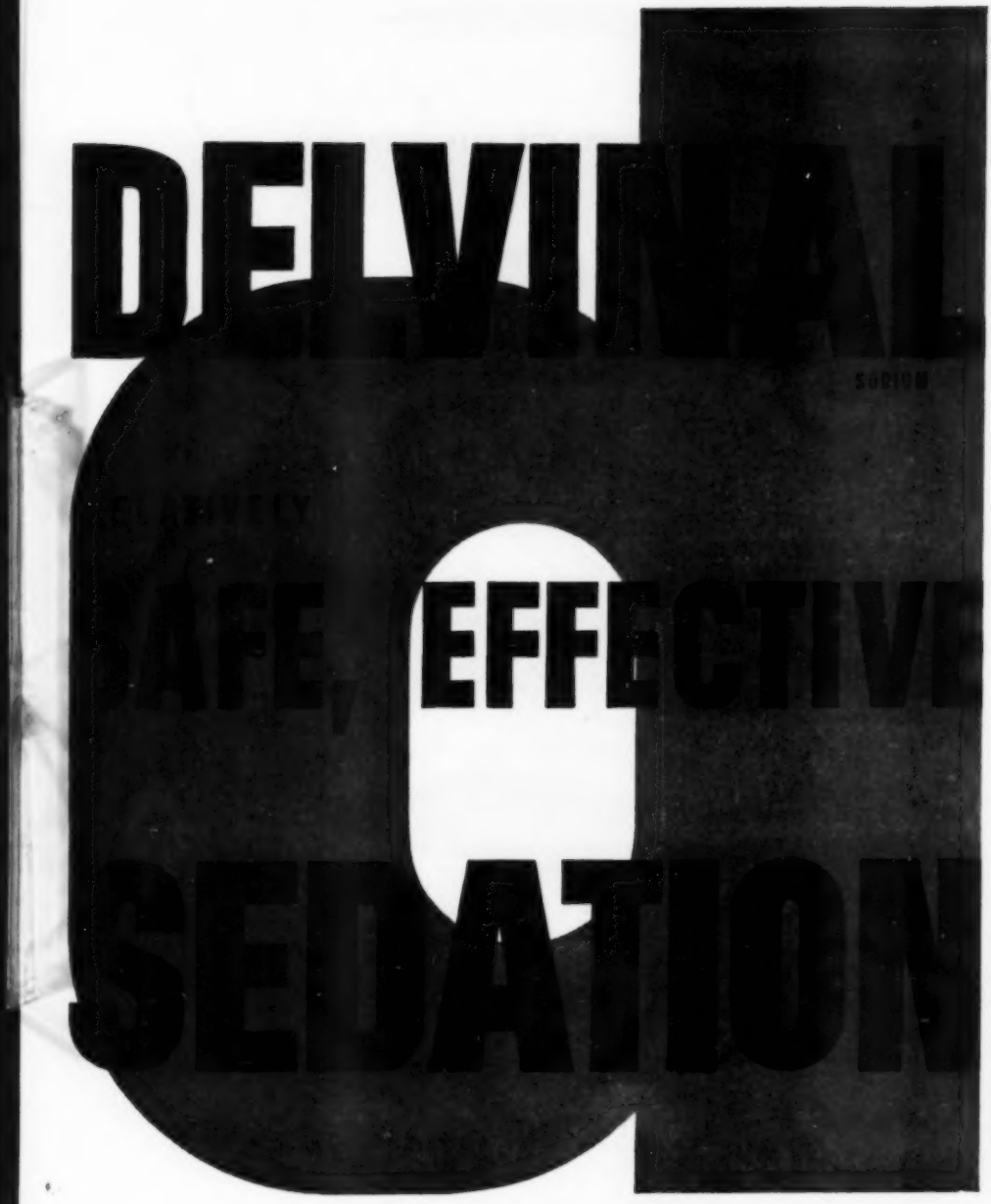

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ANNALS OF
INTERNAL MEDICINE

VOLUME 37 AUGUST, 1952 NUMBER 2

THE AMERICAN COLLEGE OF PHYSICIANS AND THE INTERNIST OF THE FUTURE*

By MAURICE C. PINCOFFS, M.A.C.P., *Baltimore, Maryland*

THE President's Convocational Address offers an opportunity to one who has been honored by this office to express his conception of the significance of the past history of the College and to formulate his opinions as to the problems that must be met in the future.

The chief purpose of the College has been and is to improve constantly the practice of internal medicine. It has exerted a powerful influence in bringing about such improvements as have already occurred.

This influence of the College has been exerted in two ways. By far the most important of these, in my opinion, has been the maintenance of a policy of high standards of admission both as to professional qualifications and as to ethics. This policy has brought into the College a type of man who would have had no interest in an organization of lower standards. Indeed, as during the last 25 years admission to Fellowship has grown progressively more difficult, there has been a constant increase in the number of young internists working and sacrificing to meet the requirements. The College has gained in strength and is accorded leadership in internal medicine, and has now to assume the responsibilities that go with leadership.

A second manner in which the College contributes to internal medicine is in its constant effort to provide facilities for the continuing education of the internist. Here, too, there has been growth. There have been expansion in the programs of the Annual Sessions, increase in the number of Regional Meetings, additional postgraduate courses, fellowships and traveling fellowships established, a publication of our own developed. All these efforts have met with astounding success. The demand uncovered calls for further expansion.

The College moves forward into the future carrying the responsibility

* Presidential Address, Thirty-third Annual Session, American College of Physicians, Cleveland, Ohio, April 23, 1952.

of leadership and pledged to the task of providing in increasing measure opportunities for postgraduate education for the internist. It is surely timely, then, to give thought to the internist of the future, he who is to be inspired to work for Fellowship, and to be aided by the educational activities of the College.

The College has an intimate concern with how internists will be trained, how numerous they will be and what will be their rôle in the medical care of the public.

As to training, if we are to predict the future we must briefly review the past.

The major portion of postgraduate education has been carried on in the hospitals where men acquire knowledge and experience as interns and residents. It may surprise some of you to know that at the turn of the century less than 20 per cent of medical graduates (the exact number is not known) took an intern year before entering practice. In 1913 a survey by the Council of Medical Education indicated that approximately 70 per cent spent an intern year in a hospital. Certainly since 1920 only an occasional graduate fails to serve as an intern.

Residency training as a significant factor was of even later development. In broad terms, it may be said that residency training arose to meet the demand for the adequate training of specialists.

Long after the attractions of practice in a specialized field had resulted in many men restricting their practice, the importance of adequate training in the special field was not recognized, nor was there any attempt by the profession to define what adequate training was. Eventually the American Medical Association, in coöperation with the national societies of the various specialties, studied this question and through the various Boards defined and recommended an adequate course of postgraduate training appropriate for each specialty. Training in hospital—residency training—was an essential feature in these programs. In the case of internal medicine a period of three years of medical residency was recommended.

It might have been supposed that these lengthy programs of training would have discouraged specialization, or have been ignored, since they were in no sense compulsory. Those who thought so underestimated our young men. No sooner was the high standard set by the American Board of Internal Medicine than the demand for medical residencies and their supply began a rapid increase.

Let me give you a few figures. In 1927 there were only 220 residencies in internal medicine available in the United States; in 1937, 10 years later, the number had increased to 437, i.e., it had only doubled in 10 years. This was the year the American Board of Internal Medicine really began to function. In the following 14 years, up to 1951, the number of medical residencies in internal medicine rose from 437 to 3,873, a ninefold increase. Indeed, by 1951 the available residencies exceeded the number of applicants

but, even so, there were in that year almost 3,000 young physicians undergoing residency training in internal medicine.

This great and rapid increase in the number of medical residencies has been accompanied by changes in the character of the residency. Since a large percentage of the Residents expect eventually to come before the Board for a written and a practical examination, they demand more instruction during their residency than is obtainable by the apprenticeship to attending men of older days. As a result there has been a great expansion, especially in the nonteaching hospitals, of such formal exercises as history meetings, clinical pathological conferences, seminars, grand rounds, etc.

I think you will agree that this change has been of benefit not only to the medical Residents but perhaps even more to the attending men upon whom this load of teaching falls. We, too, are spurred to constant study to keep our teaching and our practice abreast of the times, and are forced to analyze our experience and to formulate the lessons we have learned. The outcome of this newer type of residency training is better medical service to the public.

The part played by the medical schools in improving the quality of medical residencies should be emphasized. In general the programs of residency training in the school hospitals have served as models which have been followed as far as facilities and personnel permit in the nonteaching hospitals.

From the school hospitals also has spread the interest in research. The investigative spirit today burns like a flame in our medical schools and institutes, and sparks have spread and caught in many nonteaching hospitals. Contact with research in his own hospital environment is an invaluable stimulus to the young Resident.

It would not be realistic to leave this subject of hospital training without pointing out that its very rapid development in the last 14 years has led as an inevitable consequence to great unevenness of quality in the training offered by different hospitals. The demand for residency training in medicine and the advantage to the hospital staff of having such young associates living in the hospital have perhaps led too many hospitals to establish medical residencies. Perhaps too many inadequate residency positions have been approved by the American Medical Association. Five hundred fifty-nine hospitals now have such approval.

If we consider these hospitals as postgraduate schools—the greater number organized within the last 10 years—we must realize that much must remain to be done to render less unequal the value of the training they offer.

The training of young internists along the lines recommended by the Board is put to a test in the examinations conducted by the Board. There has been a regrettably high percentage of failures in these examinations and, as a result, there has been criticism of the methods of examination. Indeed,

some have advocated that the passage of this examination should no longer be a requirement for Fellowship in this College.

Now when there is a high percentage of failures it is wise to try to determine what part of the blame lies with instruction, what part with the student and what part with the type of examination. It is my belief that the critics of the Board examinations have not given due weight to the part played in these failures by (1) faulty training in the hospital, and (2) inadequate study and review by the physician. In addition, however, there exists, as in all examinations, a percentage of errors in the passing and in the failing. Should the College because of this error decide that it cannot require certification as an evidence of adequate training and proficiency? Shall we, in other words, suddenly reverse ourselves in this matter—discredit the Board which we have sponsored, discredit the certification which so large a number of our Fellows and Associates have labored to acquire, and attempt to set up alternative methods for determining the professional qualifications of candidates for Fellowship?

In my opinion such action would be very radical, very unwise, and very disruptive of College solidarity. I would suggest that it would be more constructive if, as a College and as individuals, we made every effort to better the training of men preparing for these examinations. There is much to be done to better residency training in these 559 hospitals. As a College we can influence these programs through our participation in the Conference on Graduate Education and in the Joint Commission on the Accreditation of Hospitals. As individuals, by teaching, example and advice we can help our residents to profit more from their training.

Let us also, as a College, support the Board of Internal Medicine in the efforts it is making constantly to improve the character of its examination so that the percentage of error in its decisions approaches the irreducible minimum inherent in all examinations of any type. In such ways I feel that the postgraduate training which will produce the internist of the future can be improved, and that in this improvement this College and its members can play a significant part.

How numerous will internists become? From the Directory of the American Medical Association we learn that in 1940 there were, in round figures, 6,400 physicians restricting their practice to internal medicine, and by 1950 there were 11,600, an increase of 82 per cent. This is a rapid increase, but a study of the number of men now in residency training, nearly 3,000, and of the number of men coming up in 1950 and 1951 for examination by the Board, leads me to predict that by 1960 there will be on the order of 20,000 to 25,000 physicians restricting their practice to internal medicine.

How many of these men practicing internal medicine will be qualified internists by training? That we cannot tell. We can, however, say that of the 11,600 in 1950, 52 per cent had passed Board examinations and a further 25 per cent had completed prescribed training but failed the Board

examination. One may reasonably expect that by 1960 an even higher level of training qualifications will have been attained. When one considers these figures, two questions arise. Is the field of internal medicine going to be overcrowded? What should be the relationship of the American College of Physicians to this great group of practitioners of internal medicine?

We cannot answer the first question, as to overcrowding, without first attempting to estimate the potential demand for the services of these men trained in internal medicine; in other words, we must define what part in the medical care of the public will be assumed by the internist of the future. I believe that there will be agreement in roughly classifying the types of service rendered by the internist into four subdivisions:

1. Internists who treat patients in their homes, in their offices and in hospitals.
2. Internists working singly, or as members of a group, who see patients only in their offices or clinics and in hospitals.
3. Internists who restrict their practice to referred patients, in other words, serve as consultants, chiefly in their offices or in hospitals but occasionally in the home.
4. Internists who restrict their practice entirely to hospitals. Among these, one would place the internists serving in the hospitals of the Armed Forces, in the Veterans Administration, Public Health Service hospitals, and also those internists combining practice, teaching and research as full-time faculty members in our schools of medicine.

This is a rough formulation and, needless to say, there is much overlapping. Moreover, men constantly change from one category to another, which is as it should be.

Now the question naturally arises, Of these four categories, which one is growing fastest, and which one in the future will continue to grow fastest? It is my belief that there is and will continue to be the greatest demand for the men of the first category, those who, with a broad and adequate training in internal medicine, treat patients in their homes, their offices and in the hospital. More and more we are seeing, in the larger cities, men from our best schools, with excellent residency training, and often certified by the Board of Internal Medicine, entering into this field of what might be called the family practice of internal medicine. In these larger cities they are beginning to displace the general practitioner, by which I mean the man who includes in his practice obstetrics, pediatrics, and often some surgery. In not a few smaller cities, and in those towns with well equipped hospitals, the same trend is observable, more, of course, in some parts of our country than in others.

The demand is there now and will, I believe, for a long time absorb the internists we are training. When the demand slackens our students and interns will be among the first to know it, and there will be a falling off in

applications for medical residencies. The law of supply and demand will function.

No doubt there will be a steady demand for internists of the other three categories that I mentioned but it will, in my opinion, be numerically much smaller. These categories will readily become overcrowded. The basic internist of the future will be of this family physician type, the counselor and adviser in times of medical need, supplementing his services with those of other specialists and consultants, ripening in wisdom through seeing disease and functional disorders from their beginnings, progressing through study and teaching in his hospital. From this large number of men who will in coming years be practicing internal medicine must be selected the majority of the future members of the College.

Before I discuss this serious problem I wish to point out that the College can never afford to confine its membership solely to practicing internists. It must be recalled that we are not a College of Internists but a COLLEGE OF PHYSICIANS. This broader term, "physician," will serve to remind us that we need for the good of the College to have among us, taking part in our councils and participating in our work, many physicians whose chief occupation is teaching and research, public health, and other fields so essential to the progress of medicine. The men in these fields that we need are the leaders, men of established reputation. We should be constantly on the search for more of such men; we should enlist their interest and should bring them into the College by direct election to Fellowship.

As regards the relation of the College to the great body of young practicing internists, I see no reason for departing from the principles that have proved successful in the past. Let us continue gradually to raise the standards for admission to Fellowship, not to such height that only a few can attain, not so low that Fellowship will lose its incentive value and be no longer a goal young men will strive for.

Let us continue to select for Associates younger men of superior training and of high personal character and then let them demonstrate of what worth they would be to the College by observing their careers as Associates. It has appeared to the Governing Bodies of the College that our present methods of evaluating the progress made by Associates need expansion. A larger part of this task must be assumed by the Governors and their local advisers.

It is felt, too, that if the standards for admission to Fellowship are being progressively raised, the maximal term of Associateship (at present five years) must be increased to give the Associate a more adequate opportunity to demonstrate his worth.

Tomorrow at the General Business Meeting of the College an Amendment to our By-Laws will be submitted to the Fellows which, if passed, will lengthen the maximal length of Associateship to 10 years. It is my

hope that it will be approved in the meeting as it already has been by both the Governors and the Regents.

Maintenance of high standards will not deprive us of influence in the lives of those practitioners of internal medicine who remain outside our ranks. If our Fellows and Associates acquire new knowledge in the Sessions and Meetings and Courses of the College, do they not disseminate this knowledge in their hospitals and in talk with their colleagues? This College is an educational body. We members are in a sense its Faculty. We come together in large or small groups to confer and to be taught by each other and by guest speakers. That, let us say, is the intramural teaching of the College; but each of us has also a function of extramural teaching less formal but none the less important. Through our own continuing education in the College we become more valuable to other internists in our community.

This striving to learn, this willingness to give time to others in teaching, or in the organization of teaching, is an essential part of the spirit of this College. It is an unselfish spirit. In the individual who possesses it there will be also an awareness of the fact that the ultimate purpose of medicine is service to the welfare of the public, not alone through the care of illness but also by giving of his ability, his time and strength to movements for the betterment of medical care in his hospital, in his local society, and in his community. A physician who manifests in his life this unselfish spirit will not be found offending against medical ethics, for those who are unethical have selfish personal gain as their prime objective.

If we look upon ourselves as both students and faculty in this College, inspired not only to learn but also to disseminate our knowledge, then we must admit to our membership men who will carry forward this work and this spirit of the College.

They must be men of proved professional knowledge and professional achievement, men capable of profiting by and contributing to the higher branches of medical learning; but more than that, they must be men whose careers indicate that they are willing to give as well as to receive.

Selection on these principles will maintain College membership as an incentive that will appeal to all that is best in the young practitioner of internal medicine. Many will be called—far more than can be chosen by the high standards which must be maintained. But it is better to have tried and failed than not to have tried at all, better for the man and better for his community.

When the time comes that the Associate is proposed for Fellowship, he should be considered not merely on the basis of his medical knowledge but on what use he has made of that knowledge. Certification by the Board of Internal Medicine should be viewed only as evidence of a reasonable stock of medical knowledge and a certain proficiency in its use. For this purpose I feel it is indispensable; if it did not exist, a similar machinery would have to be invented. But such certification should not be viewed as more than

a basic requirement. Details of the man's medical career should be on file and be scanned for the evidence they disclose of professional distinction and of continuing medical education. His medical publications will give an insight into the quality of his mind. There should be an assessment also of the man's attitude in medicine and the part he is playing in carrying his share of the load in advancing standards in his hospital, his medical societies and as a citizen in his community.

Those who collaborate in the selection of the future Fellows of the College, the Governors and their advisers, the Committee on Credentials and the Regents hold the future of the College in their hands. In selecting an individual for Fellowship they should ask themselves not merely has this man met requirements, but also is this the type of man who has something to give to the College in its intramural educational function, in its extramural educational influence, and especially in the perpetuation of the unselfish spirit of service to others that ennobles the American College of Physicians.

RÔLE OF SODIUM IN THE FORMATION AND CONTROL OF ASCITES IN PATIENTS WITH CIRRHOSIS *

By William J. Eisenmenger, *New York, N. Y.*

The formation of ascites in patients with cirrhosis of the liver is reflected in many disturbances in the metabolism of sodium and water. Since Pick [1] summarized the early evidence bearing on the regulation of water metabolism, a great deal of information concerning the retention of sodium and water has been gathered. However, even concerning those processes most extensively studied there still remains considerable controversy. No longer can one hope to find a single mechanism initiating the chain of events leading to the accumulation of ascites. From the available evidence it has become apparent that the final production of ascitic fluid represents the end result of a complex interplay of many physiologic processes, only some of which can be considered pathologic, the remainder being homeostatic. The latter nonetheless may contribute toward the further accumulation of ascites so that they too may be considered abnormal.

An analysis of the rôle of sodium studies in the treatment of cirrhosis with ascites can perhaps best be presented by considering in turn various aspects of the following three questions: 1. What physiologic mechanisms are involved in the production of ascites? 2. What are the factors concerned in controlling the rate of accumulation of ascites by the restriction of sodium? 3. How effective is the restriction of sodium in the treatment of patients with advanced Laennec's cirrhosis who are forming ascites at a maximal rate?

The patient to whom we shall direct our attention is one with advanced Laennec's cirrhosis who forms ascites at a maximal rate. In such a patient (figure 1) all of the sodium ingested in excess of dermal and fecal loss, which is normally excreted in the urine, instead is deposited in the form of ascites.[2] Thus, as first reported by Farnsworth,[3] the major defect in the metabolism of sodium in such a patient is the virtual absence of sodium from the urine despite a normal intake of sodium. However, the subnormal concentrations of sodium found in the thermal sweat and saliva of such patients [2] indicate that the phenomenon of sodium retention is generalized rather than purely renal. Furthermore, the relatively low concentrations of serum sodium often found in these patients [2] (figure 1) suggest that abnormal renal retention of sodium is not primarily responsible for the production of ascites. Given this general summary of the disturbed metabolism

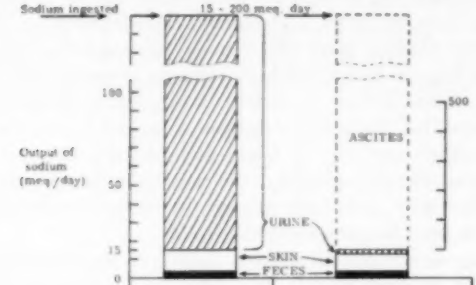
* Presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 22, 1952.

From the Hospital of The Rockefeller Institute for Medical Research, New York.

of sodium in advanced cirrhosis, we can turn to a consideration of certain of the mechanisms which may play a rôle in the production of ascites.

Renal Function

The mechanisms regulating retention of sodium by the kidneys have been investigated extensively, and the problem is far from resolved. As clearly outlined by Berliner,[4] the difficulty is largely due to the complexity of the picture, for in regard to sodium the kidney functions are multiple and include control of excretion and reabsorption of water as well as sodium, so that an adequate study of any isolated system becomes almost impossible.



	NORMAL	CIRRHOSIS WITH MAXIMAL ASCITES
Thermal sweat sodium (meq/L.)	20 - 105 (8)	2 - 60 (8)
Saliva sodium (meq/L.)	12 - 42 (15)	4 - 20 (20)
Saliva K : Na ratio	0.3 - 2.0 (15)	1.0 - 9.0 (20)
Serum sodium (meq/L.)	136 - 148	110 - 141 (50)

Fig. 1. Summary of the major abnormalities of sodium metabolism in patients with cirrhosis and maximal ascites as compared with normal values.

Studies on the relationship of sodium retention to reduced glomerular filtration rate, as originally reported by Merrill in patients with congestive heart failure,[5] have been extended by Mokotoff [6] and others, and further clarified by Pitts.[7] In accord with these observations, changes in renal hemodynamics have been considered as a possible cause of sodium retention in patients with advanced cirrhosis and ascites. Reduction in the glomerular filtration rates might well be expected in such patients, who at some stages of their disease have certain indications suggesting a deficient effective peripheral circulation, such as constantly cold extremities, a low blood pressure, peripheral venous contraction and the clinical appearance of dehydration. Farnsworth [8] found some reduction in filtration rates, as did

Sims.[9] Of particular interest, however, is the recent report of Leslie and Ralli,[10] who showed that in most of their patients who were studied while actively accumulating ascites, the glomerular filtration rates were considerably reduced, while in those patients whose ascites had previously reabsorbed the filtration rates were normal. These findings likewise applied to two patients who were tested serially until ascites was fully reabsorbed. Also, it has been demonstrated by others that small reductions in filtration rates can effect a supraproportional degree of sodium retention. Thus it appears likely that the retention of sodium and possibly of water in advanced cirrhosis may be in part attributable to the decreased filtration rate. On the other hand, the many normal filtration rates in patients with cirrhosis and ascites which were reported by Epstein [11] cannot be ignored, for these results indicate that a normal amount of sodium was delivered to the tubules and that the sodium retention manifested in these patients must have resulted from increased tubular reabsorption.

Increased Tubular Reabsorption

Concerning the mechanisms which may cause the increased renal tubular reabsorption of sodium as found in cirrhosis, again the evidence at hand is incomplete and indirect. It is well known that the adrenal steroids could produce such effects, but the degree to which these hormones are actually responsible has not been satisfactorily demonstrated as yet. There is, however, some evidence which suggests that such a mechanism is activated, and this evidence will be reviewed briefly.

In addition to the renal retention of sodium, the patient who is accumulating ascites maximally manifests marked retention of sodium in saliva and thermal sweat, and an increase in the ratio of potassium to sodium in saliva [2] (figure 1). Thus a generalized phenomenon of sodium retention is found and this suggests hormonal control. Conn [12] reports that low levels of sodium in thermal sweat may indicate an increased production of adrenal "salt active" corticoids. The low levels of sodium and the high ratios of potassium to sodium in the saliva of patients with maximal ascites possibly indicate similar hyperactivity of the salt active hormones of the adrenal cortex. This concept has some confirmation in the report of Frawley and Thorn,[13] which showed that the ratio of salivary potassium to sodium varied in direct relationship with the degree of adrenal cortical activity observed both in clinical states and as induced by the administration of the hormones.

In addition, a more direct approach to the problem was made by Bongiovanni, who attempted to demonstrate increased renal excretion of adrenal salt active hormones.[14] Reducing corticoids were found to be slightly elevated in Laennec's cirrhosis. Perhaps a more specific indication that these slight elevations reflected increases in the production of salt active steroids

was found in the further rise in urinary corticoids which occurred following further restriction of salt.

Thus, in summary, the tubular reabsorption of sodium appears to be under hormonal control, but the agent and the stimulus to its action have not been clearly established. Indirect evidence, which at present is far from conclusive, suggests that the source of the hormone is the adrenal cortex.

Pituitary Antidiuretic Hormone

In any consideration of the processes concerned in the metabolism of salt one cannot neglect certain aspects of water metabolism. The patient with cirrhosis and ascites presents obvious abnormalities in the metabolism of water. The retention of water as ascitic fluid is reflected in a small output of urine of high specific gravity. The ability to form such highly concentrated urine generally depends on an intact supraoptico-hypophyseal system, which produces the antidiuretic hormone in response to a stimulus from the osmoreceptors caused by a rise in the total osmotic pressure of the serum.

An antidiuretic substance resembling but not yet identified as the antidiuretic hormone of the pituitary has been found in the urine of patients with cirrhosis.[15, 16, 9] Assuming that this is true antidiuretic hormone, one can at present only speculate on the question of whether this increased urinary output of antidiuretic hormone reflects increased production by the pituitary or decreased inactivation by the cirrhotic liver, as was proposed by Ralli.[15] If commercial Pitressin can be compared to the antidiuretic hormone produced in vivo, the theory of decreased inactivation would not appear to be valid, for the recent report of White, Rubin and Leiter [17] indicates that the cirrhotic patient can inactivate injected Pitressin as rapidly as the normal subject. Thus one must consider the alternative theory of increased production of antidiuretic hormone. Verney [18] has shown that a small rise in the level of serum sodium stimulates the production of antidiuretic hormone, and this may occur even when the levels of serum sodium are subnormal. The depressed values of serum sodium frequently seen in patients with cirrhosis appear to represent a new level at which multiple regulatory forces have become balanced, and the production of antidiuretic hormone can be stimulated by elevation of the serum sodium above this level, even though supernormal values are not reached. In a comparison of the water metabolism in a patient with advanced cirrhosis and a normal subject, the basic differences may be summarized as follows: Each can be in a comparable state of equilibrium having quite different levels of serum sodium. The ingestion of sodium by the normal subject and by the patient results in a similar rise in serum sodium and the resultant production of antidiuretic hormone in both. The level of serum sodium falls to its previous value more rapidly in the normal subject because of the facility with which he excretes sodium, whereas the patient with cirrhosis and maximal ascites excretes virtually

none of the ingested sodium. Hence more antidiuretic hormone may be produced under the more prolonged stimulation by the elevated concentration of sodium in the patient with cirrhosis and ascites.

Reference was made above to the low level of serum sodium found in many patients with cirrhosis and ascites. Attempts to raise this level by the administration of hypertonic salt solution or to lower it still further by sodium restriction generally produce only temporary effects and readjustment is rapidly made close to the previous level. There have been some recent observations which may shed light on the regulatory mechanism which adjusts this level and permits, in certain patients with advanced cirrhosis, the maintenance of levels of serum sodium at subnormal values which, in normal subjects, would result in a cessation of antidiuretic activity, followed by a water diuresis until normal levels of serum sodium resulted. Lewis, Buie, Sevier and Harrison,[19] by a comparison of the diuretic effects of water in subjects who were either sitting or recumbent, found that a pronounced decrease in diuresis occurred in those who were sitting, and that the decrease could be partially overcome by increasing the cerebral venous pressure by means of a pressure cuff about the neck. Leaf and Mamby [20] and Strauss et al.[21] have recently reported related observations. From these results a "volume receptor" is postulated which, in response to a decreased volume of cerebral blood and extracellular fluid, stimulates continued antidiuretic activity in the presence of dilute extracellular fluid that would normally inhibit antidiuretic activity. In patients with advanced cirrhosis, as mentioned previously, despite an elevated total blood volume the peripheral effective volume appears to be reduced. Hence this mechanism of antidiuretic activity due to activation of volume receptors could be responsible for retaining water out of proportion to sodium, thereby causing the low levels of serum sodium at which many patients with advanced cirrhosis establish a new equilibrium. Thus, if it is the pituitary which responds to the volume receptors, one might then visualize the production of the antidiuretic hormone in response to two types of stimuli: one which is activated by a decrease in the extracellular fluid volume, and the other which responds to hypertonic stimulation of the osmoreceptors.

Thus far we have considered what appear to be the major physiologic mechanisms concerned in the production of ascites and in the maintenance of the volume and electrolyte content of the extracellular fluid. Figure 2 represents a summary of these mechanisms.

Control of Ascites by Dietary Restriction of Sodium

Having thus reviewed the various physiologic processes which may be active in the formation of ascites, we shall now consider how these processes are affected by the restriction of sodium. This is of particular interest because, of the four mechanisms which were considered, only one appears to be favorably affected by the restriction of dietary sodium, while the remainder

would tend to increase the production of ascites. Thus, a low salt diet probably increases the production of adrenal salt retaining hormones, decreases the blood volume and glomerular filtration rate, and increases the stimulation of the "volume receptors," and all of these factors favor antidiuresis. Opposing this tendency to retain excessive water, the only physiologic process favoring diuresis is the decreased production of antidiuretic hormone of the pituitary in response to the decreased levels of serum sodium on the osmoreceptors. The successful control of ascites by salt restriction appears to depend on whether antidiuretic activity of the pituitary can be inhibited by a degree of salt restriction which will not severely embarrass

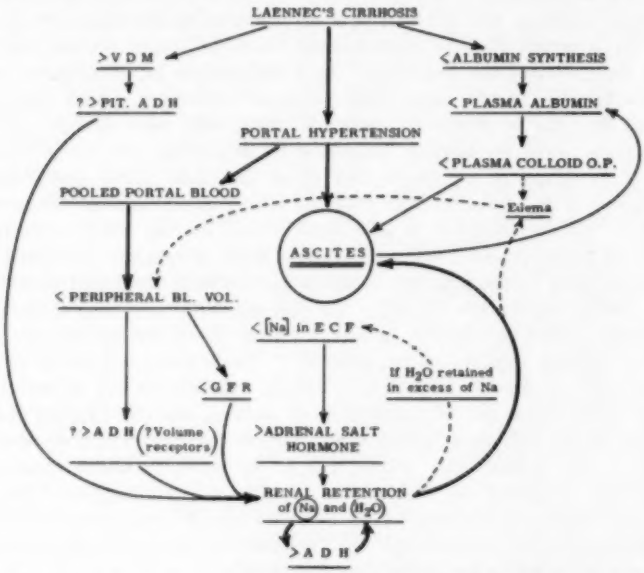


FIG. 2. Summary of major factors which appear to play a rôle in the production of ascites.

an already subnormal peripheral circulation. If the circulatory deficiency becomes dominant, then the diuretic effect of decreased antidiuretic hormone is negated by the multiple processes favoring retention of water. Then the syndrome of water intoxication develops much as was demonstrated experimentally by Elkinton, Danowski and Winkler.[22] Water is retained in excess of salt so that levels of serum sodium fall, cells become hydrated, and the patient experiences the symptoms commonly encountered in the low salt syndrome as outlined by Marriott [23] and Schroeder.[24]

In the treatment of patients with advanced cirrhosis and ascites, it is perhaps surprising that the desired degree of sodium restriction is so readily

tolerated by most patients. Thus the inhibition of antidiuretic hormonal activity is usually accomplished without excessively stimulating the complicating water retaining factors. This is illustrated in figure 3, which shows that when a patient was accumulating over 1 liter of ascites a day, Pitressin caused no further decrease in the volume or concentration of urine, thus suggesting that maximal antidiuretic activity was already in effect. On restricted intake of sodium the accumulation of ascites was completely arrested and the patient excreted a larger volume of less concentrated urine. Acute stimulation of the osmoreceptors by hypertonic salt promptly effected

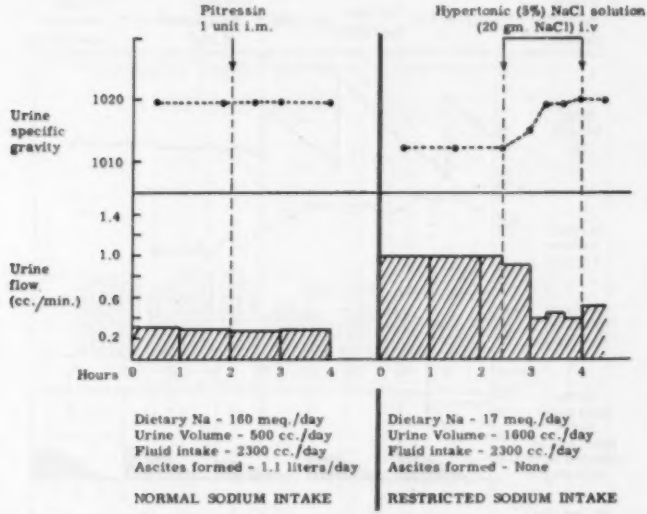


FIG. 3. Lack of additional antidiuretic activity following parenteral administration of Pitressin when patient is on normal sodium intake (suggesting maximal antidiuresis due to endogenous sources). Patient on restricted sodium intake shows reduced antidiuretic activity, and gives normal prompt antidiuretic response following administration of hypertonic salt.

a typical antidiuretic response, with a decreased minute volume of more concentrated urine. In this patient and in the one illustrated in figure 4 it would appear that water metabolism was quite normal following the restriction of dietary sodium. However, while there is no retention of water over a 24 hour period when on the low salt regimen, it is evident from the delayed excretions of acute water loads that there is still considerable abnormality in the metabolism of water of the type described by Adlersberg and Fox [25] and by Ralli [26] as a characteristic finding in patients with ascites. In each test of water tolerance there is an increase in the rate of diuresis after the first hour, suggesting that pituitary antidiuretic activity has been inhibited by the

water load. However, the subsequent diuresis was subnormal, presumably due to the activity of the other water retaining factors. A similar type of markedly delayed diuresis is seen in other situations associated with reduced filtration rates and volumes of extracellular fluid, as in Addison's disease and in the presence of pronounced depletion of sodium.[27, 22] All of the patients with ascites show this delayed excretion of water to variable degrees, and in general those patients who show the greatest delay are more likely to develop symptoms of water intoxication due to excessive cellular hydration.

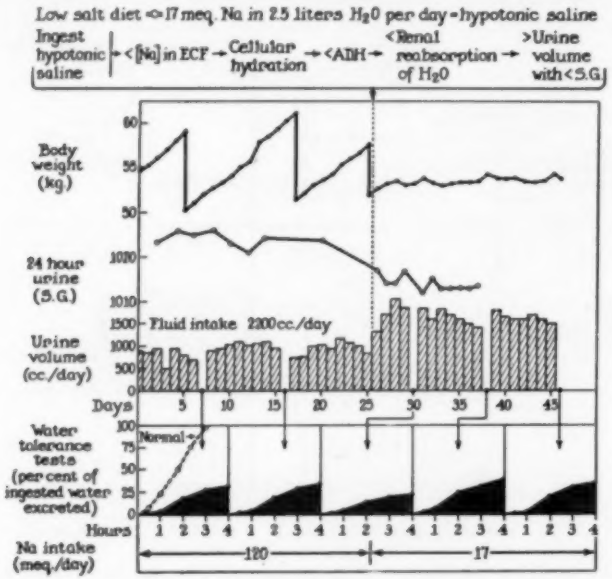


FIG. 4. Effect of sodium restriction on the formation of ascites and on the volume and concentration of urine. Acute water tolerance tests unaltered by salt restriction.

THERAPEUTIC RESULTS IN PATIENTS TREATED BY SALT RESTRICTION

Having considered certain of the factors concerned in the production of ascites and in its control by salt restriction, the clinical application of such therapy will be considered. A number of reports [28, 29, 30, 2] have indicated the therapeutic effectiveness of salt restriction as a means of controlling the formation of ascites. The present report provides a further analysis of the results in 25 patients so treated, with emphasis on the long range results. Two patients who died of esophageal hemorrhages within one month of the onset of treatment are not included in the series. The patients were treated with a diet which was restricted in sodium to approximately 17 mEq. a day.

Also, by the use of low salt whole protein supplements, a high protein diet was maintained in order to provide adequate nutritional therapy, the importance of which was first recognized by Patek.[21] These patients were selected on the basis that they had been forming ascites steadily and maximally for at least several months. Maximal formation of ascites was indicated by the virtual absence of sodium from the urine of these patients despite a liberal intake of salt. Such a patient, if given a normal intake of approximately 10 gm. of salt a day, would show a steady increase in ascites of about 1 L. per day. All of the patients in the series initially had marked abnormalities of hepatic function (table 1).

TABLE I

Laboratory Data on 25 Patients with Laennec's Cirrhosis and Maximal Ascites Treated with High Protein, Low Salt Diet

		% BSP retention[3]		Serum albumin Gms %		Prothrombin % of normal		Serum Bilirubin mg %		Zinc sulfate turbidity units	
		Initial[1]	Final[2]	Initial	Final	Initial	Final	Initial	Final	Initial	Final
	Pt. # 1	20	10	2.7	2.9	35	44	0.8	0.7	22	19
Group 1	2	23	20	2.4	2.8	43	33	1.0	1.0	15	17
(Died)	3	19	23	3.0	2.4	30	28	0.8	1.2	53	59
	4	33	45	1.8	3.1	64	54	1.3	2.7	23	20
	5	32	25	2.0	1.8	46	35	1.2	8.0	33	60
	6	31	17	3.3	3.5			2.0	1.6	30	28
	7			3.1	3.3	48	80	1.0	2.5	25	34
% abnormal		100	100	100	100	100	100	72	88	100	100
Group 2	8	34	30	2.6	3.7	68	58	1.3	2.5	6	13
(Persistent	9	27	31	2.7	3.3	73	80	1.1	1.0	25	21
Ascites)	10	29	30	2.9	4.1	63	50	1.4	1.2	33	28
	11	25		3.1	4.0	50	48	3.9	2.2	16	33
	12	19	12	1.7	3.9	80	48	0.3	0.4	18	21
	13	23	21	2.3	2.2	63	61	0.8	0.6	25	27
	14	40	41	2.3	2.8	45	38	1.3	1.2	35	40
% abnormal		100	100	100	100	86	100	72	72	88	88
Group 3	15	40	37	2.1	4.8	45	70	1.8	1.2	26	24
(Ascites	16	19	6	3.8	4.2	80	85	0.8	0.8	14	9
Reabsorbed)	17	32	7	2.1	3.8	60		0.8	0.3	22	13
	18	23	5	2.5	3.2	66	75	1.2	1.1	10	10
	19	35	2	1.7	4.1	47		2.7	0.6	28	6
	20	34	20	2.2	3.3	73	75	0.4	1.4	27	10
	21	10	5	2.9	5.0		85	0.8	0.8	15	10
	22	20	34	3.5	4.3	60	55	1.9	1.6	15	30
	23	20	6	3.2	4.6	82	75	1.0	0.8	19	20
	24	8	5	3.0	4.4	90	70	0.5	0.2	10	9
	25	32	38	2.4	4.0	52	44	3.0	1.0	21	11
% abnormal		100	91	100	63	80	22	54	45	100	38
Normal		0-4		>4.7		>70		<0.8		<12	

1. Initial indicates in initial period of observation at Rockefeller Hospital.
2. Final indicates present results in patients who are living.
3. Retention of bromsulfalein 45 minutes after a dose of 5 mg/Kg.

The accumulation of ascites was arrested adequately in all but three patients (patients 1, 2 and 9), as is indicated by the small number of paracenteses required during the period when dietary sodium was restricted (table 2). In two of these patients (patients 1 and 2) symptoms of water intoxication occasionally developed, and accordingly an increased intake of sodium was allowed at intervals. Despite hyponatremia which, when present, was often temporarily aggravated by salt restriction, the remainder of the patients responded well to the low sodium diet in that they showed no signs of salt deficiency and had prompt and sustained increases in urinary

TABLE II

Summary of Clinical Data on 25 Patients with Laennec's Cirrhosis and Ascites Treated with a High Protein Diet and Salt Restriction

	Pt. #	Sex	Age[1]	Duration of[2] Disease (months)	Duration Maximal[3] Ascites (months)	Duration Sodium[4] Restriction (months)	No. of taps while Sodium restricted	Cause of Death	Abnormalities of liver[5] function tests	
									Initial	Final
Group 1 Died	1	M	53	42(32)	27	30	10	Peritonitis	++++	++++
	2	F	55	60(16)	55	9	6	Esoph. hem.	++++	++++
	3	F	40	120(90)	24[6]	24[6]	0	Post operative	++++	++++
	4	M	48	11(7)	9	6	1	Hepatoma	++++	++++
	5	M	57	60(35)	13	12	0	Esoph. hem.	++++	++++
	6	M	53	25(10)	12	8	0	Cholemia	++++	++++
	7	M	64	45(15)	16	15	0	Esoph. hem.	++++	++++
								Present status of ascites[7]		
Group 2 Persistent Ascites	8	F	40	60(38)	10	7	0	Minimal	++++	++++
	9	M	50	42(18)	27	15	4	Maximal	++++	++++
	10	M	51	24(20)	18	20	0	None for 3 mos.	++++	++++
	11	M	51	50(37)	25	12	0	Minimal	++++	++++
	12	M	64	31(19)	22	19	0	Maximal	++++	++++
	13	M	59	24(12)	23	10	0	Maximal	++++	++++
	14	M	60	20(18)	19	16	0	Minimal	++++	++++
								Interval free of ascites on normal diet (months)		
Group 3 Ascites reabsorbed	15	F	40	85(83)	14	7	0	66	++++	+++
	16	M	48	47(43)	9	6	0	36	+++	+
	17	M	52	28(23)	12	7	0	10	++++	++
	18	F	36	38(26)	9	6	0	16	++++	+
	19	M	62	51(47)	7	4	0	38	++++	+
	20	M	54	60(48)	20	11	3	24	+++	+++
	21	F	43	42(30)	11	8	1	30	+++	0
	22	M	64	32(28)	11	6	0	19	++++	++++
	23	F	53	22(15)	10	6	1	10	++++	++
	24	M	38	130(20)	36	10	0	12	+++	++
	25	M	66	27(16)	10	10	0	10	++++	+++

1. Age at which first signs of cirrhosis appeared.
2. Duration of disease from first sign of disease until the present time or until death (Group 1). Figure in parentheses indicates period of observation at Rockefeller Hospital or clinic.
3. Maximal ascites, indicated by almost complete absence of sodium from urine (<3 mEq./day) or by gain averaging 1 liter per day when on normal salt intake.
4. During period of maximal ascites accumulation, dietary sodium limited to 17 mEq. day.
5. Estimated from table 1, giving approximately 1+ for each abnormal result up to 4.
6. Intermittent.
7. Minimal indicates some ascites, but rigid salt restriction unnecessary because of increased urinary sodium.

volume so that no further ascites formed. The extent of the metabolic aid which such control of ascites can provide may be appreciated if one considers that the protein content of approximately 200 c.c. of blood plasma is lost in the accumulation of each liter of ascites. Perhaps the continuous conservation of body protein effected by the prolonged control of the formation of ascites constitutes the major beneficial effect of salt restriction.

Of the 25 patients treated, seven died (group 1, tables 1 and 2), seven have persistent ascites (group 2), and 11 have shown marked clinical improvement (group 3). The patients who died never showed any significant laboratory indication of improvement. The patients with persistent ascites (group 2) likewise have shown no significant degree of improvement in hepatic function, with the exception of some increases in the levels of serum albumin. In terms of clinical improvement the second group is mixed. Three of the patients persist in their tendency to form ascites maximally, while four of the group now tolerate increased intakes of salt (3 to 4 gm. a day) without increasing the volume of ascites present. The improved tolerance of salt is reflected in increased amounts of sodium in the urine of these patients. The third group includes those patients who eventually became

clinically well, although initially they resembled the other patients in that they formed ascites at a maximal rate for from seven to 36 months. Now for from 10 to 44 months they have been free of ascites and of other hepatic symptoms while on a normal diet. It is of interest that none of the patients who maintained this degree of improvement for over six months has thus far shown any indication of regression. The clinical improvement in the patients of the third group is reflected in most instances by significant improvement in the laboratory tests of hepatic function.

Thus one can say that the low salt diet, as applied both in the hospital and at home, is readily tolerated by most patients with advanced Laennec's cirrhosis. By its use one can avoid the trouble and potential hazards and the constant waste of plasma protein that are consequences of numerous paracenteses. As to any improvement in the prognosis of patients so treated, one can only surmise that these general therapeutic aids may produce prolonged metabolic improvement which in certain cases may mean the difference between recovery and death.

Summary

An analysis has been presented of the physiologic mechanisms which appear to be involved in a complex system leading to the production of ascites in patients with advanced Laennec's cirrhosis. A general pattern of this system has been presented. The control of ascites by the restriction of sodium appears to be due to a decreased production of antidiuretic hormone. The subject of "volume receptors" has been discussed, along with considerations of how this mechanism may partly account for the depressed levels of serum sodium often seen in severe cirrhosis. Finally, data were presented summarizing the clinical results in 25 patients with cirrhosis and ascites who were treated with a diet high in protein and low in sodium.

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DIABETIC RETINOPATHY *

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Diabetic retinopathy had been recognized by Jaeger in 1855,[1] and well described and differentiated, both clinically and pathologically, by Nettleship as early as 1877.[2] There ensued a period, however, when no sharp clinical boundaries were defined between this disease picture in the fundus and those attributed to atherosclerosis, hypertension and renal disease. This difficulty was due only in part to the limitations of ophthalmoscopy. More confusing was the frequent association of these disease processes in the same patient and the inadequate laboratory tests available. Moreover, the tendency of clinicians to attribute any retinopathy found in diabetic patients to the diabetic process, or, alternatively, to attribute the retinopathy of diabetics to atherosclerotic or hypertensive mechanisms, further obscured the differentiation.

In recent years, retinal vascular pathology has been greatly advanced by the study of flat preparations of whole retinas,[3] and the visualization of their entire vascular trees by special staining [4] and injection [5] technics. By the application of these methods the basic pathology of diabetic retinopathy has been reëstablished. A clear cut and rather specific pathologic entity of diabetic retinopathy is thus defined. From these findings a much more lucid concept of the clinical picture of diabetic retinopathy can be formulated.

This may be best illustrated by reference to figures 1 and 2 of flat preparations of diabetic retinas stained with periodic acid-fuchsin. We see great numbers of discrete saccular aneurysmal dilatations of capillaries, occasionally thin-walled, but frequently enclosed in thickened laminated layers of hyaline material. In some instances a hyalinized nodule taking the mucopolysaccharide stain almost obliterates the lumen of the capillary. The microaneurysms are found mostly in the deeper capillary layer. Surrounding these aneurysms are exudates and hemorrhages, which are at least partly explained by leakage of proteins and red cells through the walls of the aneurysms. Marked distortion of capillary pattern, as well as newly formed capillaries on the surface of the retina, and tufts of capillaries extending forward into the vitreous are found in the more advanced stages of the disease.

It is true that capillary aneurysms, per se, are not unique to the diabetic process. They are found in venous occlusion,[6] malignant hypertension,[7] pernicious anemia,[8, 9] chorioretinitis, and in the extreme periphery of some normal retinas,[10] but differing as to number, size, morphologic appearance, and location from those of diabetic retinopathy. Although atherosclerosis

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or hypertension may be present, the pathologic picture in the diabetic retina is readily recognizable by the characteristic pattern of numerous aneurysms with surrounding exudates and hemorrhages. Furthermore, diabetic retinopathy can be found with no evidence whatsoever of arteriolosclerotic or atherosclerotic lesions.[11] Diabetic retinopathy is further identified as a

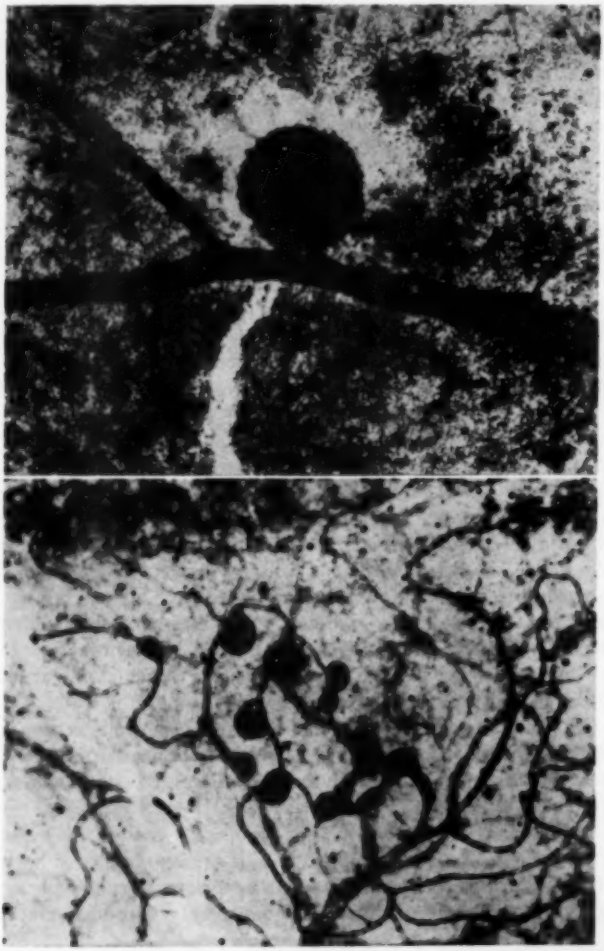

FIG. 1. Flat preparations of human diabetic retinas stained with periodic acid-fuchsin. (*above*) Single discrete thick-walled capillary aneurysm. (*below*) Cluster of capillary aneurysms.

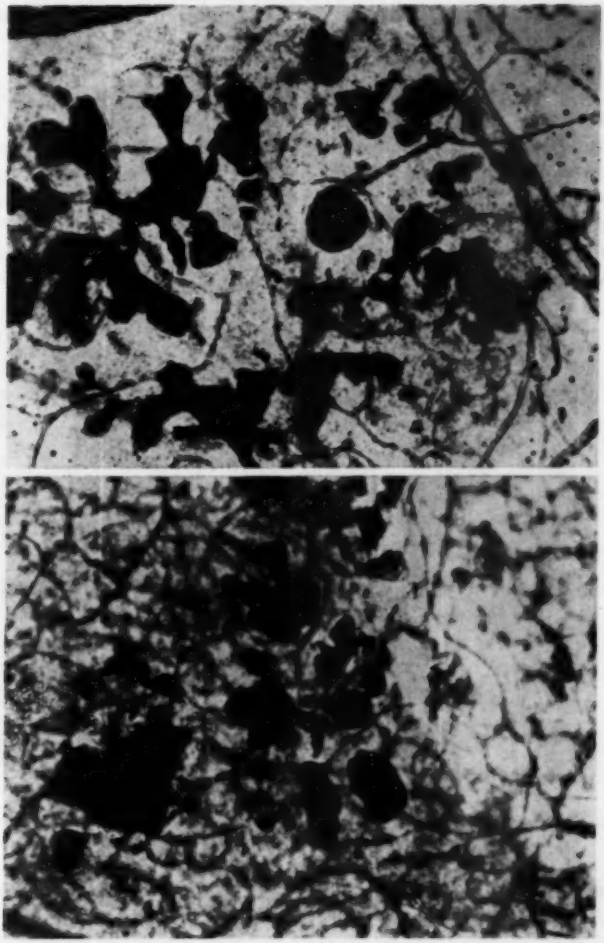

FIG. 2. Flat preparations of human diabetic retinas stained with periodic acid-fuchsin. Capillary aneurysms surrounded by hemorrhages and exudates.

definite and separate disease entity by the remarkable statistical correlation between the occurrence of diabetic retinopathy and the Kimmelstiel-Wilson lesion in the kidneys of the same diabetic patients, as found at autopsy.[5, 11, 12, 13] The similarities between the pathologic pictures of Kimmelstiel-Wilson lesions in the kidney and diabetic retinopathy are even more impressive.

Aneurysmal dilatations of capillaries and hyalinized globular or laminated nodules with identical staining characteristics are demonstrated in both organs (figure 3).[14]

In the light of these investigations, the progress of diabetic retinopathy as visualized ophthalmoscopically becomes somewhat clearer. The disease is in general progressive, but is characterized by relapses and spontaneous remissions at irregular time intervals. The earliest changes seen are usually punctate microaneurysms of capillaries, singly and in clusters, in and about the macula. These tend to occur in crops, becoming more numerous and surrounded by small exudates and hemorrhages (figure 4). The true microaneurysms tend to persist for weeks and months, whereas the extravasations

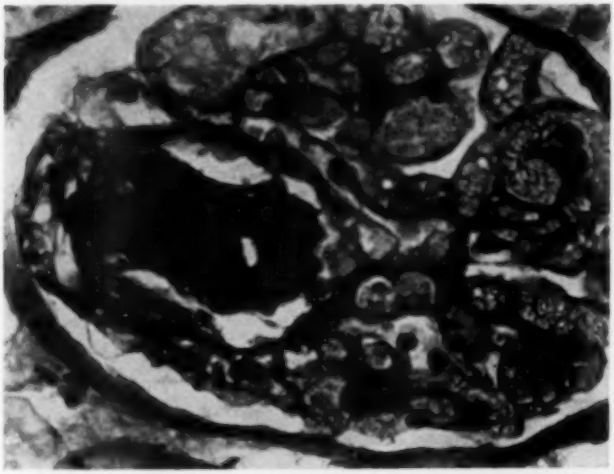

FIG. 3. Kimmelstiel-Wilson lesion in kidney of a diabetic patient. Note hyalinized nodule in glomerulus.

can resorb in a few days. Thus, on repeated examinations or fundus photographs, one finds the same punctate "petechiae" persisting for many weeks. Finally, they become hyalinized and are then either invisible ophthalmoscopically, or are seen as discrete punctate white dots. Further progression of the disease leads to larger and more numerous hemorrhages with confluent exudates. Seventy-five per cent of cases never go past this stage, even with long duration.[15] In the advanced stages of the disease one sees scarring of the retina, distortion of capillary pattern and new formation of capillaries in the retina. Hemorrhages into the vitreous are followed by organization and vascular ingrowth, known as "retinitis proliferans" (figure 5). Contraction of these fibrous bands may lead to retinal detachment. All of this

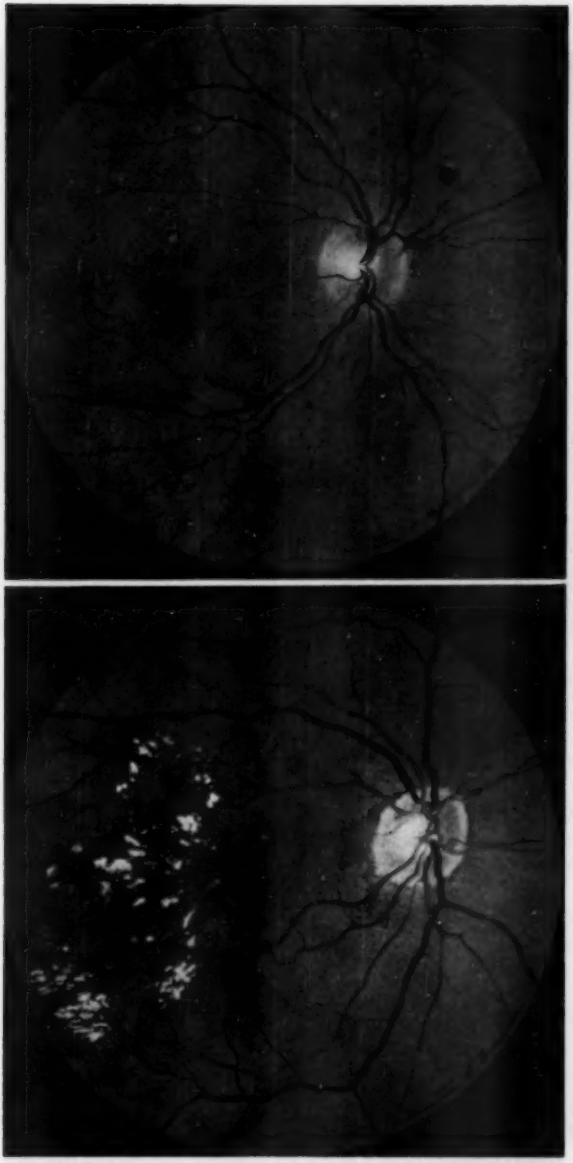

FIG. 4. Drawings of the ophthalmoscopic picture of diabetic retinopathy. (*above*) Early diabetic retinopathy with few scattered aneurysms and hemorrhages. (*below*) Later stage with aneurysms surrounded by hemorrhages and exudates.

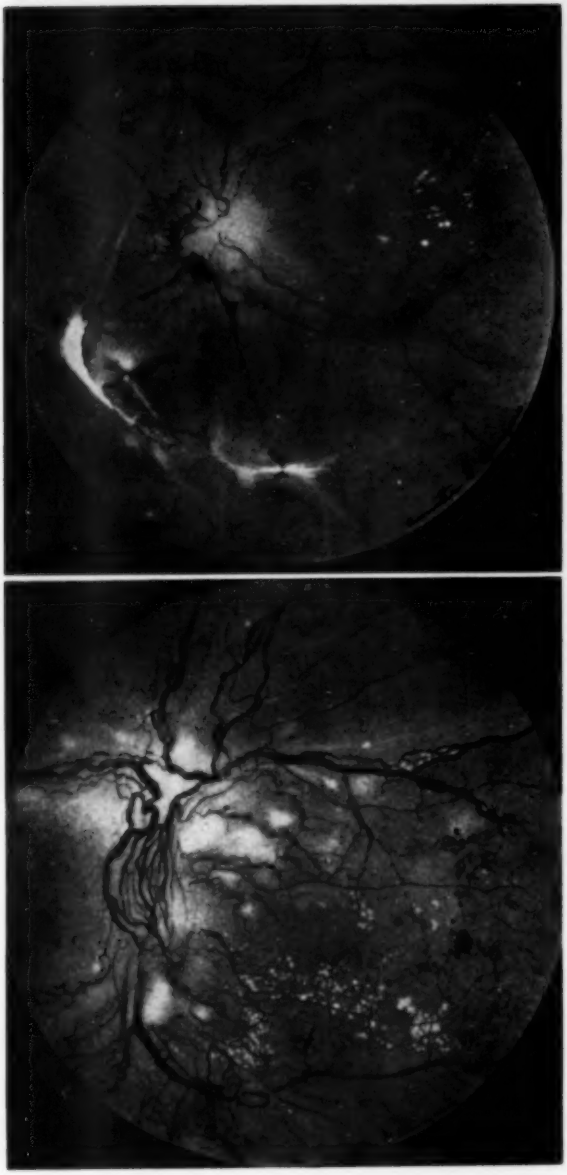

FIG. 5.

FIG. 5. Drawings of the ophthalmoscopic picture of diabetic retinopathy. A. Hemorrhage into vitreous with beginning proliferative changes. B. Marked retinitis proliferans with hemorrhages and exudates as well as capillary aneurysms. C. Advanced retinitis proliferans.

can occur in the absence of associated hypertension, atherosclerosis, renal disease or retinal edema.[8, 13, 16, 17]

In diabetic patients with diabetic retinopathy and Kimmelstiel-Wilson kidney lesions, the capillary aneurysms in the retina can be readily seen and studied ophthalmoscopically. This provides a particularly valuable approach to the evaluation of the course and therapy of these patients. Various empiric attempts to treat diabetic retinopathy have been unsuccessful, and are extremely difficult to evaluate because of the very irregular progression of the disease and the long spontaneous remissions. Clinical correlations of diabetic retinopathy and renal lesions with the duration rather than the severity of the diabetes,[16, 17, 18, 19] and with its control,[15, 20, 21, 22, 23, 24] are valuable and have added greatly to our knowledge. They have not been too fruitful, however, in revealing the causative factors in the progression of this disease. Certainly insulin deficiency, hyperglycemia and glycosuria are not the entire story, and other endocrine, nutritional and metabolic disorders must play a rôle.[25, 26, 27, 28]

In a disease entity such as diabetic retinopathy, where the clinical and pathologic pictures are now clearly defined, intensive work is needed in the

study of the etiologic factors and pathogenesis. It is only then that a rational approach to therapy can be expected. The experimental production of diabetic retinopathy would provide a method of attacking these problems.

With the knowledge that animals are capable of forming capillary aneurysms,[6] we have recently turned our attention to the experimental production of diabetic retinopathy in rabbits. These experiments were carried out in collaboration with Dr. Jonas Friedenwald. They were based on our observations and those reported in the literature [22] of the appearance of diabetic retinopathy in the absence of hypertension in diabetics during pregnancy, and its disappearance after delivery. Lawrence [29] reported two carefully followed cases which first developed diabetic retinopathy during pregnancy and cleared completely following delivery. We have seen two quite similar cases and, in addition, one case of very early diabetic retinopathy which advanced rapidly during pregnancy, and regressed spontaneously to its original level following delivery. These observations suggested that the increased endogenous ACTH during pregnancy might play a rôle in the pathogenesis of diabetic retinopathy. Lesions resembling capillary aneurysms clinically in the fundi of two patients * have been observed to appear during treatment with intravenous ACTH for sarcoid, and to disappear following cessation of ACTH. Furthermore, Lukens and Dohan [30] have reported Kimmelstiel-Wilson lesions in the kidneys of a dog made diabetic for five years by injections of anterior pituitary extracts.

Rabbits made diabetic with alloxan and injected with ACTH † were found clinically to develop an ophthalmoscopic picture resembling early diabetic retinopathy. At autopsy, examination of flat preparations of the retinas of some of these rabbits revealed definite capillary aneurysms as well as distortion of capillary pattern (figure 6). These findings simulate early diabetic retinopathy closely, but to date we have seen none of the advanced manifestations of the disease. Lesions similar to those described by Kimmelstiel and Wilson were also found in the kidneys of these experimental animals (figure 7). These experiments are in progress and will be reported in detail elsewhere.[31] Previous attempts to obtain diabetic retinopathy with alloxan alone were unsuccessful.[32] Although rabbits given cortisone [33] or compound F [34] alone developed Kimmelstiel-Wilson-like kidney lesions, no retinal lesions were apparent with the dose levels given. These early observations immediately suggest a new method for the study of the development of diabetic retinopathy and Kimmelstiel-Wilson kidney lesions.

The present tentative working hypothesis is that both the pancreatic lesions and the action of ACTH in amounts that are excessive *for a diabetic*, are factors in the development of both diabetic retinopathy and Kimmelstiel-Wilson lesions in the kidney. This concept of the histogenesis of diabetic retinopathy offers a reasonable explanation for many scattered reports.

* Patients of Dr. Howard Naquin.

† The ACTH (corticotrophin) used in these experiments was kindly supplied by Dr. H. F. Hailman, of the Upjohn Company, Kalamazoo, Michigan.

In the diabetic, it is understandable that the increased ACTH output occurring in pregnancy, infection or poor control should lead to retinopathy. The rapidly increasing incidence of diabetic retinopathy is well established.[19] This is due partly to the fact that diabetics are living longer with insulin and

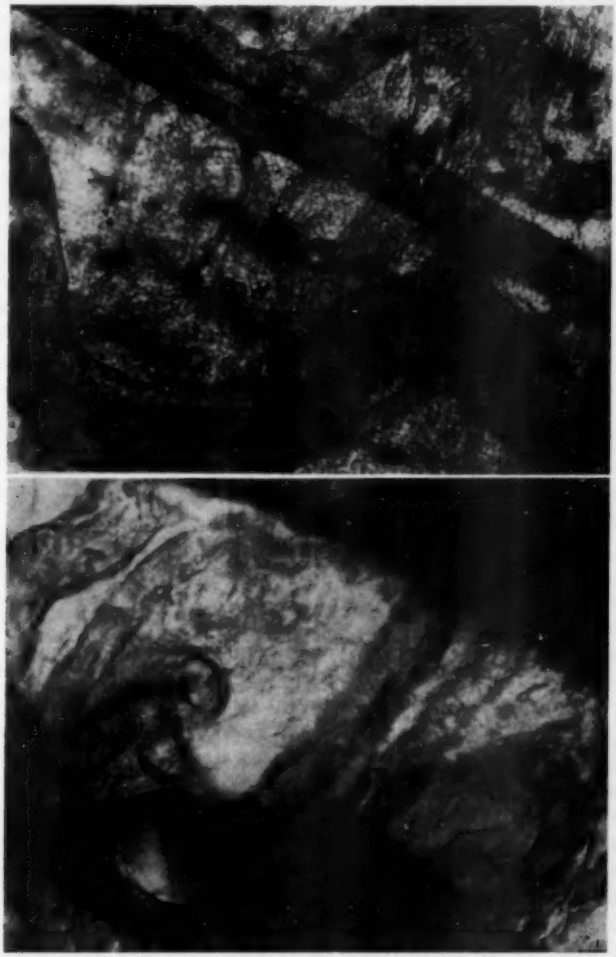

FIG. 6. Flat preparation of retina of a rabbit made diabetic with alloxan and given ACTH for three weeks. (*above*) Capillary aneurysms and distortion of capillary pattern. (*below*) High-power view of capillary aneurysm above. Note afferent and efferent capillaries of the aneurysm.

better care, but may also be explained by the excessive stress of recent years. Vogelius' [35] study, for example, showed an increased incidence of diabetic retinopathy in Denmark during the war years. We may also account for the occasional case that develops full blown classic diabetic retinopathy before the diabetes is evident by clinical examination or laboratory test, including the glucose tolerance test.[36]

Furthermore, it is reasonable to find occasional "normal" retinas with a few capillary aneurysms, and to find capillary aneurysms in the retinas of a few cases treated with large doses of ACTH. Rich [37] has recently found lesions resembling those described by Kimmelstiel and Wilson in the kidneys

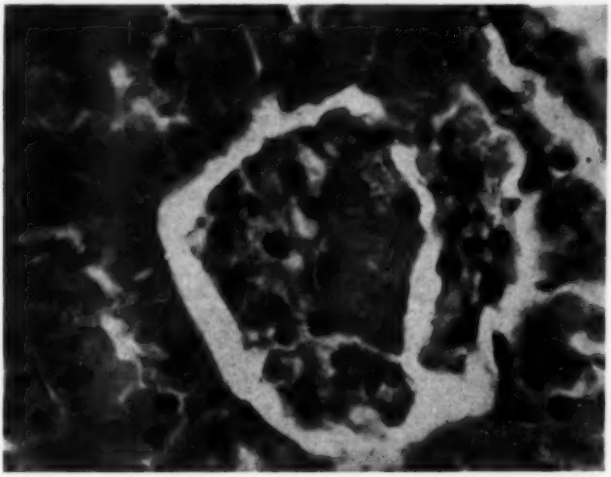

FIG. 7. Lesion resembling the Kimmelstiel-Wilson lesion found in kidney of same rabbit as figure 6. Compare with figure 3.

of a patient treated with intravenous ACTH. Clusters of capillary aneurysms have been found at autopsy in flat preparations of the retinas of some cases of adrenal hyperplasia.[25]

Zubrod et al., [39, 40] in an excellent study of a large series of diabetics with and without Kimmelstiel-Wilson lesions, noted marked clinical differences between these two groups. The Kimmelstiel-Wilson group showed a remarkable absence of acidosis, even in the presence of marked hyperglycemia. They suggested that the clinical and anatomic differences between these two groups were related to metabolic differences. Kinsell and co-workers [41] have noted a marked diminution in fasting-induced ketonuria and hyperketonemia in diabetic patients as a result of the administration of ACTH or cortisone. Thus we have additional evidence that the differences between

diabetics with Kimmelstiel-Wilson lesions and those without this complication can be explained by a *relative excess* of certain adrenal cortical secretions in the former group or a *deficiency* in the latter.

The close interdependence between the function of the adrenal cortex and the beta cells of the pancreas in man has been well recognized by Thorn and co-workers.[42] They pointed out that primary dysfunction of either of these tissues is often correlated with compensatory functional changes in the other. Thus, they described islet atrophy in Addison's disease and decreased adrenal cortical activity in some diabetics. Miller and Mason [43] found that 17-ketosteroid excretion was decreased in some diabetics without complications, as compared with normals, but that there was no correlation with the severity of the diabetes. Talbot and co-workers [44] noted low output of urinary water-soluble copper-reducing corticosteroids in controlled diabetic patients. We could find no reports of measurements of adrenal cortical activity in diabetics with diabetic retinopathy and Kimmelstiel-Wilson kidney lesions, compared with similar tests in diabetics with neither retinopathy nor intercapillary glomerulosclerosis.* Such comparisons should provide the testing ground for the proposed theory.

The weights of the whole adrenals at autopsy are influenced by many factors, and are an admittedly poor method of evaluating adrenal cortical activity. It was remarkable, therefore, to find an average weight for a group of 22 cases with proved Kimmelstiel-Wilson kidney lesions 24 per cent higher than for a group of 23 cases of diabetes without the Kimmelstiel-Wilson lesion.[45] This led us to the histologic examination of the adrenals of a series of 155 diabetics with and without Kimmelstiel-Wilson lesions,† and 91 non-diabetics of the same age group.

The first and most obvious changes we noted between the two diabetic groups were the presence or absence of at least one low-power microscopic field of lipoid-laden vacuolated cells in the zona fasciculata of the adrenal cortex. Figure 8 shows examples of the two groups. There is evidence that it is the zona fasciculata that has most to do with secretion of carbohydrate-regulating principles,[46] but the significance of the amount of lipoid present in the cells at autopsy is not entirely understood. Although the immediate effect of ACTH is a marked reduction in lipoid in the adrenal cortex, it seems likely that the prolonged administration of ACTH results in hypertrophy and increased lipoid secretion in the zona fasciculata.[47, 48] Of all cases, 93 per cent fell sharply into one or the other of these groups; 7 per cent could not be classified because of elements of both groups, autolysis or other disease processes. The results are recorded in table 1. In the 64 diabetics with Kimmelstiel-Wilson lesions, 55 (86 per cent) had lipoid

* Shadaksharappa et al.[51] have reported increased excretion of phosphomolybdate-reducing substances in three cases of Kimmelstiel-Wilson disease and normal values for five diabetics. There was decreased 17-ketosteroid excretion in both groups of diabetics.

† Dr. S. L. Eversole, of the Department of Pathology, The Johns Hopkins Hospital, classified the kidneys of this series of diabetics into the two groups.[40]

vacuoles, three (5 per cent) had no vacuoles, and six (9 per cent) were unclassified. Of the 91 diabetics with no evidence of Kimmelstiel-Wilson lesions in the kidney, 11 (12 per cent) had lipoid vacuoles, 76 (84 per cent) no vacuoles, and four (4 per cent) were unclassified. The 91 nondiabetics were divided on the basis of their adrenal histology into 68 (75 per cent)

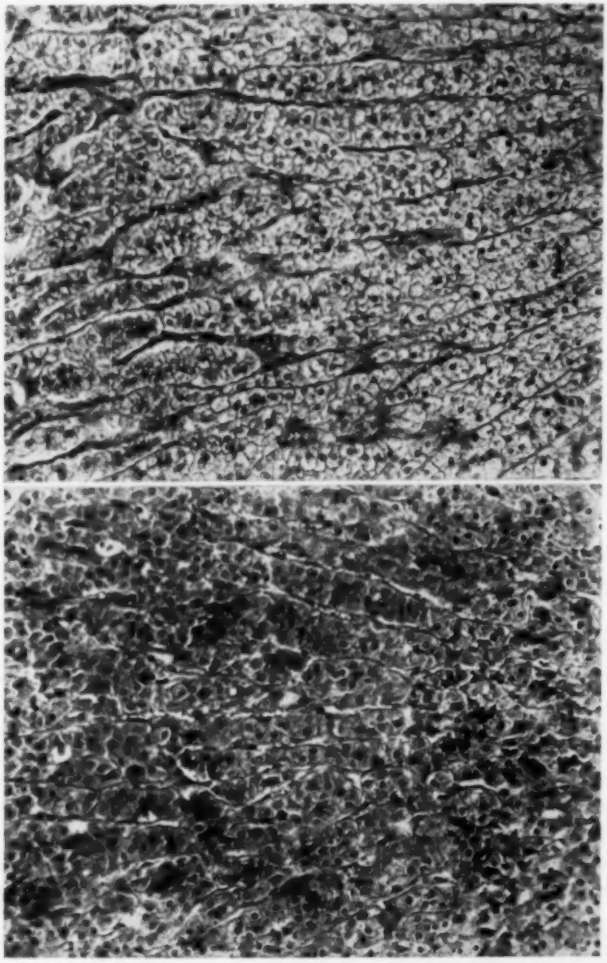

FIG. 8. Human adrenal cortex (H. and E. stain). (*above*) Vacuolated zona fasciculata. (*below*) Non-vacuolated zona fasciculata.

TABLE I

Lipoid Vacuolation of Zona Fasciculata of Adrenal Cortex

	Vacuolated	Nonvacuolated	Unclassified
91 diabetics without K-W	11 (12%)	76 (84%)	4 (4%)
64 diabetics with K-W	55 (86%)	3 (5%)	6 (9%)
91 nondiabetics	68 (75%)	16 (17%)	7 (8%)

K-W = Kimmelstiel-Wilson disease.

with lipoid vacuoles, 16 (17 per cent) with no vacuoles, and seven (8 per cent) unclassified. These results will be reported in detail elsewhere.[48]

It is difficult to be sure that all cases of Kimmelstiel-Wilson lesions in the kidney and vacuolation in the adrenals have been recognized, since in many of the older cases only one microscopic section of each tissue was examined. Furthermore, the findings in the adrenal cortex may be related only to the progression of the disease at the time of death, and not to the older lesions already present in the kidneys. Therefore, the remarkable statistical correlation in diabetics of the Kimmelstiel-Wilson lesions with a vacuolated adrenal cortex is most impressive.

It is true that many factors can influence the secretory activity and vacuolated appearance of the adrenal cortex. One of the important things contributing to the appearance of the adrenal cortex at autopsy is the cause of death. It has been well demonstrated that severe infection can produce a nonvacuolated adrenal cortex, whereas sudden death (e.g., an automobile accident) is more likely to result in a vacuolated adrenal cortex.[48, 49] It was therefore necessary to review these 246 cases from the point of view of cause of death. In table 2 there is tabulated a comparison of cause of death with appearance of the adrenal cortex in each of the three groups. Of the classified cases dying of severe infection (Group I), 65 per cent of nondiabetics and 96 per cent of diabetics without Kimmelstiel-Wilson disease fell into the nonvacuolated group, whereas only 12 per cent of Kimmelstiel-Wilson cases

TABLE II

Relation of Vacuolation of Zona Fasciculata to Cause of Death in Classified Diabetics and Nondiabetics

Cause Death	Diabetics without K-W		Diabetics with K-W		Non-diabetics	
	Vacuolated	Non-vacuolated	Vacuolated	Non-vacuolated	Vacuolated	Non-vacuolated
I	1 (4%)	25 (96%)	15 (88%)	2 (12%)	6 (35%)	11 (65%)
II	5 (11%)	39 (89%)	24 (96%)	1 (4%)	45 (90%)	5 (10%)
III	5 (29%)	12 (71%)	16 (100%)	0 (0%)	17 (100%)	0 (0%)

I = Severe burns, traumatic shock or hemorrhage, severe infection (septicemia, peritonitis, meningitis, etc.).
II = Chronic debilitating disease, carcinoma, chronic infection.
III = Cardiorenal disorders or sudden accidental death.
K-W = Kimmelstiel-Wilson kidney lesions.

were so classified. On the other hand, when death was attributed to cardiorenal or sudden accidental death (Group III), 100 per cent of Kimmelstiel-Wilson disease and 100 per cent of nondiabetics were found to have a vacuolated zona fasciculata, whereas only 29 per cent of diabetics without the Kimmelstiel-Wilson lesion fell into this group. Those classified patients dying of chronic debilitating disease, carcinoma or chronic infections (Group II), were equally as convincing in demonstrating the remarkably decreased incidence of vacuolation (11 per cent) in the diabetics without Kimmelstiel-Wilson lesions, and the excessive incidences of lipoid vacuoles (96 per cent) in the Kimmelstiel-Wilson group. Although all diabetics have an increased incidence of sepsis before death (28 per cent of Kimmelstiel-Wilson and 29 per cent of diabetics without Kimmelstiel-Wilson, as opposed to 19 per cent of non-diabetics are in Group I), this cannot account for the differences found. Therefore, we may conclude that the immediate cause of death does not appear to explain the correlation in diabetics of lipoid vacuolation of the zona fasciculata with Kimmelstiel-Wilson disease in the kidney.*

Speculation at this early stage in our studies is admittedly hazardous, but the absence of lipoid vacuoles in the uncomplicated diabetic may perhaps be interpreted as a compensatory decrease in adrenal cortical capacity for certain activities. Normal or relatively excessive adrenal cortical capacity in the diabetic would then characterize, or perhaps be related to the causation of, the Kimmelstiel-Wilson lesion. At any rate, the division of diabetics into two groups on the basis of adrenal histology, and its close correlation with the separation on the basis of renal and ocular pathology are very real findings. It will be important to interpret and confirm this relationship by means of adrenal cortical function tests in living diabetics of both groups.

Such work is now in progress, and preliminary results are most encouraging. For example,† the diabetic with diabetic retinopathy has an adrenal cortex responsive to exogenous ACTH as measured by eosinophil counts, whereas the adrenal cortex of some diabetics without retinopathy responds less readily or not at all to this ACTH test. This failure to respond to exogenous ACTH in some of the cases free of retinopathy must be related to defective function of the adrenal cortex, since the same patients do get a fall in eosinophils following a cortisone injection. Therefore, we have additional evidence for a marked difference in some aspects of adrenal cortical activity between these two groups. A much more detailed investigation of adrenal cortical function in diabetics of both groups is indicated.

Although no reasonable therapy is evident at this moment, the possible cure of diabetic retinopathy by means of bilateral adrenalectomy reported by Green is of great interest.[50] The findings reported above give us grounds

* It is conceivable that diabetics without Kimmelstiel-Wilson disease die in such fashion as to deplete the lipoid content of their adrenals. If proved, this would also constitute a difference between the two groups of diabetics.

† These tests were performed with Dr. Richard Hoover, of The Wilmer Opthalmological Institute.

for the hope that we are much closer to rational means of preventing and treating this disease.

Summary and Conclusions

1. Diabetic retinopathy is a separate and discrete disease entity which can be recognized both clinically and pathologically and is not dependent upon any hypertensive or atherosclerotic process.

2. The renal lesions described by Kimmelstiel and Wilson are closely correlated at autopsy in occurrence, appearance and staining characteristics with the lesions of diabetic retinopathy.

3. A picture strikingly similar to early diabetic retinopathy and the Kimmelstiel-Wilson lesion can be produced experimentally in alloxan diabetic rabbits by the injection of ACTH. An opportunity is thus afforded for a careful study of the pathogenesis of this disease process and for an evaluation of the effects of various means of therapy.

4. In diabetic patients at autopsy, there is an apparent correlation of lipoid-laden vacuolated cells in the zona fasciculata of the adrenal cortex with the Kimmelstiel-Wilson lesions in the kidney. In those diabetics without Kimmelstiel-Wilson lesions, there is a markedly decreased incidence of lipoid vacuoles in the adrenal cortex as compared with the non-diabetic, or with the diabetic with Kimmelstiel-Wilson lesions. We have been unsuccessful so far in explaining these changes on the basis of the cause of death.

5. An attempt has been made to formulate a tentative working hypothesis regarding the possible relation of some adrenal cortical functions to the occurrence of diabetic retinopathy and intercapillary glomerulosclerosis in the diabetic. Some of the relevant literature and experimental and clinical observations supporting this concept have been presented. It should be emphasized that such a hypothesis has not been established. It is presented in the hope of stimulating various workers, using a wide variety of tests, to conduct critical comparative studies of adrenal function in diabetics with and without retinopathy.

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ACUTE BARBITURATE INTOXICATION: A STUDY OF 300 CASES BASED ON A PHYSIOLOGIC SYSTEM OF CLASSIFICATION OF THE SEVERITY OF THE INTOXICATION *

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INTRODUCTION

THE importance of the problem of acute barbiturate intoxication has been well recognized in recent years, but the clinical evaluation of therapy has been hampered by lack of a system of classification of the severity of the poisoning. The use of one plan of treatment or another has often been advocated on the basis of a small series of cases in which some patients might well have recovered under any plan of treatment.

We shall make no attempt to review the voluminous literature on the subject but refers the interested reader to the excellent review of Koppanyi and Fazekas.[1] These authors stressed the need for a classification of the severity of intoxication. They advocated that cases be selected for picrotoxin therapy on the basis of prior observations of the response to the use of Metrazol.

Roche, Wynne and Haskins [2] reported the treatment of three cases correlated with blood levels of barbiturate. The technical difficulty of this determination places it beyond the range of practicality for most institutions.

The present study is divided into two parts. The first is a review of all cases treated at this institution from January, 1940, to July, 1949. During this time there were 209 cases, treated in many different ways by many different physicians. The second part is a study of 91 cases treated from July, 1949, to April, 1951. During this time a standard system of therapy was used.

CLASSIFICATION OF SEVERITY OF COMA

As a prelude to our study we devised the following classification of severity of barbiturate poisoning, based primarily on the degree of depression of the central nervous system, the respiration and the circulation. This classification is not entirely original. It is basically the classic stages of anesthesia, which we have modified slightly and adapted to this problem.

Group O: A patient who is asleep but can be roused and will answer questions, sit up in bed, drink fluids, etc.

* Received for publication January 23, 1952.
From the First Medical Division, The Roosevelt Hospital, New York, N. Y.

Group I: A patient who is comatose but will withdraw from painful stimuli such as venipunctures, slapping, pinching, etc. There is no circulatory embarrassment, and all reflexes are intact.

Group II: A patient who does not withdraw from painful stimuli but has no respiratory or circulatory depression. Most or all of the reflexes are intact.

Group III: A patient most or all of whose reflexes are absent, but who is without depression of respiration or circulation.

Group IV: A patient most or all of whose reflexes are absent, and who has respiratory depression, with cyanosis, or circulatory failure and shock, or both.

It is important to emphasize that grouping of a patient should not be done until an adequate airway has been established, because cyanosis and areflexia may be secondary to anoxia on an obstructive basis. When oxygenation is reëstablished the patient will be in a lighter group than he appeared at first.

In evaluating reflexes, primary emphasis should be given to the tendon reflexes. We have found the pupillary and especially the corneal reflexes very often deceptive. Contrary to classic teaching, our experience has been that often the corneal reflex is the first to disappear and the last to return.

Results of First Part

With this classification as a basis we shall present the 209 cases treated from January, 1940, to July, 1949. Table 1 shows the yearly incidence and mortality of barbiturate poisoning. Over the period of the study the incidence has been steadily rising, a fact which has caused public health authorities much serious thought. The yearly mortality varied from 0 to 22 per cent, and averaged 13.4 per cent. There were 28 deaths.

Table I

Year	Admission	Fatalities	Per Cent
1940	1	0	0
1941	9	2	22
1942	8	1	12
1943	9	0	0
1944	26	4	15
1945	23	3	13
1946	41	5	12
1947	47	4	8
1948	30	6	20
1949 (6 Months)	15	3	20
Total	209	28	13.4%
1949–50	52	2	3.8
1950–51 (9 Months)	39	3	7.7
Total	91	5	5.5%

Table 2 shows the incidence by sex and age. Two-thirds of the patients were women. The peak incidence is in the third, fourth and fifth decades of life.

TABLE II

Incidence by Age and Sex

		Under 14	14–19	20–29	30–39	40–49	50–59	60–69	70–79	80–85	Unknown	Total
Part 1	M.	1	2	13	19	13	18	8	1	0	0	75
	F.	0	0	33	51	24	12	7	3	2	2	134
Total		1	2	46	70	37	30	15	4	2	2	209
Part 2	M.	0	0	4	5	8	5	4	0	0	0	2
	F.	1	2	15	17	14	9	3	4	0	0	65
Total		1	2	19	22	22	14	7	4	0	0	91
Total		2	4	65	92	59	44	22	8	2	2	300

Figure 1 shows the number of cases and fatalities in each group. The majority of the cases were in groups I and II, while most of the deaths were in groups III and IV. We shall have more to say about the deaths in groups I and II later.

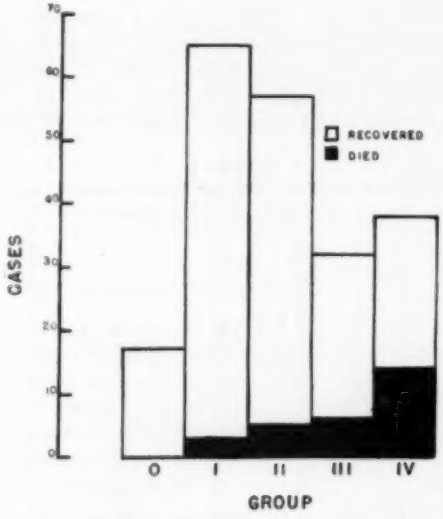

FIG. 1. Distribution of cases by group in first part.

In 152 of the cases the identity of the drug was known. In 57 it was pentobarbital, in 35 Seconal, in 31 phenobarbital, in 22 Amytal, in three Tuinal (a mixture of half Seconal and half Amytal), and in nine it was other barbiturates.

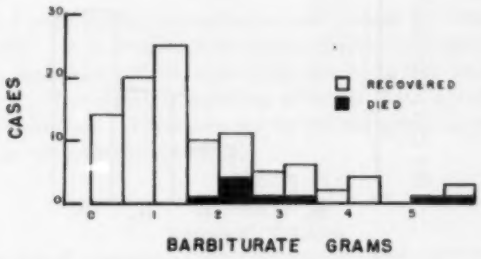

FIG. 2. Distribution of cases by amount of barbiturate taken.

In 107 cases, history of the amount taken was available (figure 2). It is seen to vary widely. An attempt to estimate the minimal lethal dose was handicapped by the fact that only nine of the 28 total fatal cases were included. With one exception, all patients known to have taken less than 2 gm. recovered.

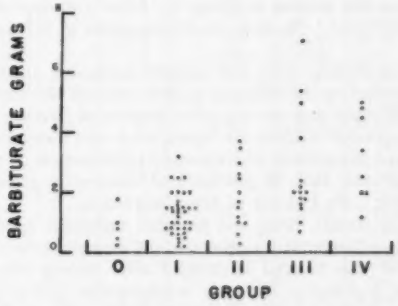

FIG. 3. Note the lack of correlation between dose of barbiturate, length of coma and depth of coma.

An attempt was made to correlate the length and depth of coma with the amount of drug ingested. The random scattering on figure 3 demonstrates that no correlation can be made. There are apparently too many other variables, as was pointed out also by Koppanyi and Fazekas.[1] In addition, we could find no correlation between the amount of drug ingested and the prognosis.

There is a good correlation, however, between depth of coma and prognosis (figure 4). The percentage of mortality increases with severity of coma.

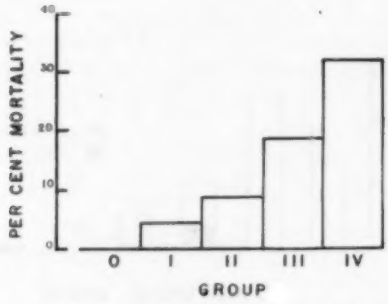

FIG. 4. Mortality according to group. Note the correlation between prognosis and depth of coma.

Since a fatal outcome should not be expected in groups I and II, we shall summarize the fatal cases in these two groups.

1. A 29 year old female who took 3.3 gm. of phenobarbital entered in group II, never roused from coma but died with a cardiac arrhythmia after 34 hours of therapy. She received 730 mg. of amphetamine and 33 gm. of caffeine.

2. A 55 year old male with cirrhosis, cholemia and jaundice took an unknown amount of barbiturate and entered in group I. After two days without improvement he was started on analeptics. He developed tachycardia of 160 and died on the fourth day.

3. A 63 year old female, drug and amount unknown, entered in group II and responded at first but died on the fifth day of cholemia and bleeding esophageal varices.

4. A 57 year old male took an unknown amount of Sodium Amytal and entered in group II. He responded initially but lapsed back into coma and died on the fourth day. Autopsy showed pneumonia and myocardial infarction.

5. A 63 year old male took 10 gm. barbital, entered in group II, and died in 60 hours from pneumonia. He had not received antibiotics.

6. A 60 year old female, drug and amounts unknown, entered in group I, but died in three days from metastatic carcinoma and hematemesis.

7. A 22 year old male entered in group I after having taken 3 gm. of Seconal. He was given 22 mg. picrotoxin, 1,150 mg. amphetamine, 89.5 gm. of caffeine and 575 mg. of ephedrine in 27 hours. He developed tachycardia and a terminal fever of 104.8° F.

8. A 56 year old male, a known hypertensive with chronic cardiac failure, entered in group II after having taken an unknown amount of Phanodorn. He was given 48 mg. of picrotoxin, 40 gm. of caffeine and 723 mg. of amphetamine in 24 hours. His blood pressure fell and 24 hours after admission he developed a ventricular tachycardia which did not respond to intramuscular quinine, but progressed to a fatal ventricular fibrillation.

Study of these eight cases reveals a very interesting fact. Most of them were in the sixth and seventh decades and all died of causes other than direct

effect of the barbiturates. Three of them died of preëxisting diseases after recovery from poisoning.

Two died of pneumonia. We feel that these cases might have been saved by more meticulous bronchial toilet, including bronchoscopy, and by the use of prophylactic antibiotics, which were not available at the time these cases were treated.

Three died with cardiac arrhythmias, and one of the other patients also had tachycardia. It is possible that these arrhythmias might have been produced by the analeptics caffeine and amphetamine, which had been given in large amounts. The direct stimulating effect of these agents on the myocardium is well known. Therefore, we turned our attention to all cases who died of cardiac arrhythmias (table 3).

TABLE III

Tachycardia Fatalities

Case No.	Amount of Barbiturate gm.	Group	Hours of Treatment	Picrotoxin mg.	Amphetamine mg.	Caffeine gm.	Remarks
1	?	IV	36	321	0	31.5	Pulse 160, "weak." Temp. 104.
2	?	III	31	460	0	26.5	Pulse 176. Died in circulatory collapse.
3	2.4	III	60	42	0	43.0	Pulse 240. Temp. 104.4.
4	3.0	III	72	102	200	20.5	Pulse 208. Responded at first. Lapsed into coma after tachycardia.
5	?	IV	31	30	230	23.0	Pulse 140, irregular; heart stopped before respiration.
6	?	IV	49	285	210	14.0	Pulse 120, irregular.
7	?	IV	35	0	625	43.0	Pulse 120, gallop rhythm.
8	?	II	25	48	723	40.0	Pulse 170; terminal ventricular tachycardia and fibrillation.
9	3.1	II	34	0	730	33.0	Pulse 124, irregular. Died "cardiac" death.
10	3.0	I	27	221	1,150	89.5	Pulse 140, temp. 104.8.
11	?	I	72	33	340	16.0	Pulse 160. Cirrhosis, uremia.
12	?	III	15	0	720	20.0	Terminal tachycardia and circulatory collapse.
13	?	IV	40	313	1,000	1.0	Developed tachycardia after 20 hrs. treatment; died 20 hrs. later.
14	?	III	96	575	75 (Ephedrine)	12.5	Pulse 160. Died of pneumonia.

Unfortunately, electrocardiographic documentation was obtained in only a few cases, but ventricular tachycardia was demonstrated in one of the cases in which electrocardiograms were taken. It is noted that these cases had all received huge doses of caffeine or amphetamine, or both.

We next tabulated those cases who recovered and were given more than 6 gm. of caffeine or 300 mg. of amphetamine in any one 24 hour period

TABLE IV

Non-Fatal Cases with Large Doses of Caffeine or Benzedrine

Case No.	Amount of Barbiturate gm.	Group	Hours of Treatment	Picrotoxin mg.	Amphetamine mg.	Caffeine gm.	Apex Rate	Arrhythmia
1	3.0	II	42	54	580	12.5	120	Sinus tachycardia.
2	?	II	28	0	20	20.0	112	Sinus tachycardia.
3	8.0	IV	33	33	0	21.0	140	Auricular tachycardia.
4	1.5	II	12	9	310	20.0	120	Many PVC's.
5	10.0	III	8 days	50	1,070	35.0	160	Auricular tachycardia.
6	?	III	75	54	940	15.0	>140	Auricular tachycardia and PVC's.
7	0.8	IV	40	100	120 (Ephedrine)	31.0	122	Sinus tachycardia.
8	?	IV	12	9	200	13.0	140	Auricular tachycardia.
9	0.6	II	18	12	100	15.0	116	Sinus tachycardia.
10	?	IV	50	60	400	7.5	200	Sinus tachycardia.
11	?	IV	60	36	880	8.5	176	Gallop rhythm.
12	?	IV	48	78	540	3.0	110	Sinus tachycardia.

(table 4). It will be seen that all developed arrhythmia of one kind or another; over half were serious arrhythmias with rates of 140 or above.

Because of these findings we concluded that, in the doses used, these drugs exert a powerful stimulus on the myocardium which may lead to a fatal arrhythmia in a patient who might otherwise recover. We therefore set a tentative upper limit of 6 gm. of caffeine and 300 mg. of amphetamine per 24 hours as the safe dose of these drugs.

TABLE V

Causes of Death

Central nervous system	
Depression	7
Hyperthermia	1
Respiratory	
Pneumonia	5
Obstruction	1
Cardiovascular	
Arrhythmia	14
Failure or infarction	3
Incidental	3

Table 5 represents the immediate cause of death as determined clinically or by autopsy. The total adds up to more than 28 because in several cases more than one cause was considered responsible.

It is to be noted that in only seven cases was depression of the central nervous system by barbiturate a significant cause of death. In all other cases death was caused by complicating pneumonia, arrhythmias, cardiac failure or infarction, and by incidental diseases such as carcinoma and cirrhosis. One of the fatal cases had a terminal hyperthermia to 106°, unaccompanied by any significant infection, clinically or at autopsy.

This case was a 76 year old woman who had taken an unknown quantity of barbiturate and entered with a temperature of 106°. She was classified in group IV.

She had been in coma for about 24 hours. She died before treatment could be instituted.

This hyperthermia is very reminiscent of that sometimes seen in cerebral hemorrhage. In addition, two of the cases who died with pneumonia had fever to 107°, which seemed to be out of proportion to the extent of the pneumonia. It is interesting to speculate that this hyperthermia may have been induced by action of the barbiturates on the heat regulating center in the hypothalamus. Another possible explanation is cerebral damage from prolonged anoxia.

Treatment

On the basis of these findings, and after consideration of the treatment recommended by other authors,[1-10] we set up the following program of therapy based on our classification of the severity of coma.

There are certain general measures which apply to all cases. First and foremost, these patients must be carefully observed. Blood pressure, pulse, respirations and reflexes should be recorded at least every half-hour, and can conveniently be recorded in tabular form along with medications, fluids and other pertinent observations.

Meticulous attention must be paid to the airway. A pharyngeal airway should be kept in place as long as the gag reflex is depressed, and at the slightest indication of laryngospasm (very common in these patients) an endotracheal tube should be inserted. The bed should be placed on shock blocks to facilitate drainage of secretions, and excess secretions should be removed by suction. If aspiration of vomitus occurs, bronchoscopy should be done immediately. Atropine can be given to reduce secretion, but there is danger of producing inspissated mucous plugs. The patient should be turned from side to side to prevent hypostatic pneumonia, and should be given prophylactic penicillin. Turning also helps to prevent the characteristic blisters these patients often develop over pressure points. In all patients except those in extremis a gastric lavage should be done even though the drug was taken many hours previously. In large quantities the barbiturates cause local gastric irritation and pylorospasm, and important amounts of the drug may remain in the stomach for many hours. A saline cathartic should be left in the stomach in an attempt to reduce absorption of the drug remaining in the bowel.

The fluid balance must be maintained as with any unconscious patient. The barbiturates are eliminated to a variable extent by the kidneys, and so adequate urinary output must be maintained. There is some experimental evidence that barbiturates are antidiuretic agents,[11] and so the mercurial diuretics may be useful, but their value has not been established. These patients are often alcoholics with variable impairment of liver function, and since these drugs are partially detoxified by the liver, parenteral vitamin B

complex and glucose should be given. In addition, a continuous slow infusion affords a convenient route for the administration of analeptics.

If arrhythmias develop, they should be treated appropriately. Intravenous procaine is effective in stopping ventricular arrhythmias, while also affording a weak analeptic action.

In addition to the above general supportive therapy, we advocate the following use of analeptic drugs. It should be kept in mind in using these drugs that they are extremely powerful agents, and that caffeine and amphetamine especially have profound side effects on the cardiovascular system. We would like to emphasize that the following schedules represent the maximal dosage. In acquiring experience with caffeine and amphetamine, we have come to feel that optimal dosage is lower than these limits. These drugs should be stopped if any arrhythmia occurs.

With these reservations, this is the standard procedure we have followed:

Group O and I. These patients should all recover without analeptics. They must, of course, be closely observed lest they lapse deeper into coma.

Group II. These patients will probably recover spontaneously, but recovery may be hastened and complications lessened by treatment with analeptics. We give caffeine and sodium benzoate in doses up to 0.5 gm. every two hours, not to exceed 6 gm. in 24 hours, and/or amphetamine 25 mg. every two hours, not to exceed 300 mg. in 24 hours.

Group III. Many of these patients will die without analeptics. Caffeine and amphetamine should be given as above. If these measures do not restore reflexes within 15 to 20 minutes, picrotoxin should be used. A knowledge of its pharmacologic properties is essential to its proper use. Picrotoxin acts primarily on the spinal and medullary centers, unlike caffeine and amphetamine, which act primarily on higher centers. Picrotoxin is very quickly eliminated from the circulating blood and cannot be detected after about 10 minutes, and its effect is apparent for only about 30 minutes. On the other hand, the onset of its effect occasionally is rather mysteriously delayed for 10 to 15 minutes, and its injection should not be repeated too frequently for fear of masked cumulative toxicity. Therefore, it should be given every 20 to 30 minutes. The object of its use is to stimulate the return of reflexes, not the return of consciousness. Muscular twitching is a warning sign that the dose is too large and should be reduced. The optimal dose is that just short of the amount required to produce twitching and is different in each patient, and in a given patient varies from time to time. The administration of this drug is the personal responsibility of the physician and should not be delegated to the nurse. To arrive at the optimal dose we give 1 c.c. (3 mg.) intravenously and observe the result. If twitching or return of reflexes does not occur we increase the next dose to 2 c.c. (6 mg.), again observing the result. The dose is thus increased in a stepwise direction until the desired result is obtained. The patient must be reëxamined before every dose to be sure that warning signs of twitching have not

developed, since overdosage will cause convulsions. Should these convulsions occur the temptation to give sedation must be strongly resisted, because usually they are of short duration, and only if they last long enough to cause anoxia should they be treated with sodium pentothal (not sodium phenobarbital, because of its slower elimination). Used in this manner, picrotoxin is a relatively safe drug and has been given in quantities up to 14.0 gm.[7]

Group IV. Caffeine, amphetamine and picrotoxin are given as for group III, but larger doses of picrotoxin are usually necessary, and we start with 6 to 9 mg. and increase the dose more rapidly.

We have not mentioned oxygen previously because anoxia is not a serious problem in groups O-III. Of course, oxygen should be given to all but the mildest cases, and can be given without fear of adverse effects in groups I-III. However, in group IV patients with respiratory depression and anoxia, the administration of oxygen alone may be dangerous for two reasons: First, that with the respiratory center depressed by barbiturate, the only stimulus to respiration may be anoxia acting through the carotid body, and with the relief of anoxia by oxygen this stimulus is removed and respiration ceases; second, that an intratracheal catheter may supply adequate exchange of oxygen across the alveolar membrane, but without adequate ventilatory motion of the chest, carbon dioxide will not diffuse and a severe respiratory acidosis may result. The already depressed respiratory center will be further narcotized by carbon dioxide. For these reasons, patients in group IV with any but the mildest respiratory depression should be given artificial respiration. We have used both the Drinker and the chest type of respirator with good results.

If the patient is in shock, blood should be drawn for typing and cross matching immediately. The above treatment measures will often bring the blood pressure back to normal, but transfusion may be necessary. Neosynephrine (10 mg. per liter) or nor-epinephrine (1 mg. per liter) given in a continuous infusion is often of value in bringing the blood pressure back to normal when amphetamine does not.

Many drugs have been advocated in the therapy of barbiturate coma. Metrazol has much the same pharmacologic effects as picrotoxin and probably is of value.[10] We have had no experience with it. Nikethamide has been reported to be ineffective,[8] as has sodium succinate.[9]

It is of course of extreme importance that these patients receive proper psychiatric treatment following their recovery from the acute intoxication. Discussion of this treatment is beyond the scope of this paper.

Results of Second Part

The above schedule was put into effect in July, 1949. Since then there have been 91 cases admitted to the Roosevelt Hospital. Table 2 shows the distribution by age and sex.

Figure 5 shows the distribution of cases according to group. This is essentially the same as the distribution of cases prior to July, 1949.

The drug taken was known in 80 cases. In 26 cases it was pentobarbital, in 25 Seconal, in nine phenobarbital, in seven Amytal, in nine Tuinal, and in four it was other barbiturates.

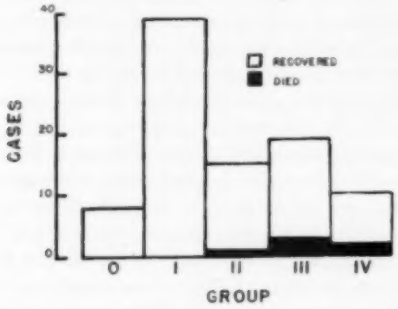

FIG. 5. Distribution of cases according to group in second part.

Figure 6 shows the amount taken by group. It will be noted that there is so much overlap that the dosage is not a guide to prognosis in an individual case. Naturally, there is a trend to more severe depression with higher dosage.

We were of course interested to see the incidence of arrhythmias (table 6). Electrocardiograms were taken before treatment was started, and arrhythmias were recorded electrocardiographically. There were nine cases of premature ventricular contractions, with coupling in three of these. These

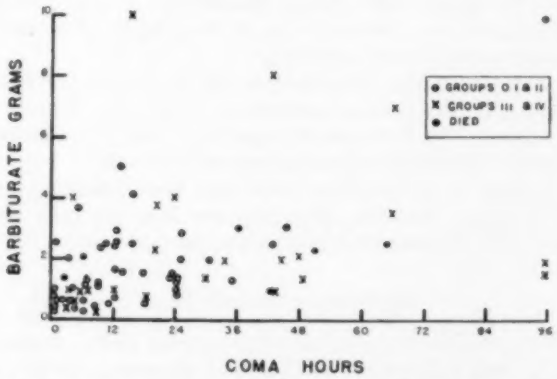

FIG. 6. Correlation between amount of barbiturate taken and depth of coma.

arrhythmias were considered indications for stopping caffeine or amphetamine. One of the cases of coupling was promptly controlled by quinidine lactate, and one by intravenous procaine hydrochloride in a dose of 4.5 gm. over a period of seven hours. Two other cases received procaine for frequent premature ventricular contractions.

The third case of coupling was clearly due to picrotoxin at a dosage level of 30 mg. every 30 minutes. It would disappear about 15 minutes after a dose of picrotoxin, only to return immediately following the next injection. After the cause of the arrhythmia had been established, picrotoxin was stopped and the arrhythmias ceased. In this case no caffeine or amphetamine had been given. One case developed many premature ventricular

TABLE VI

Arrhythmias, 1949–1951

Case No.	Amount of Barbiturate gm.	Group	Hours of Treatment	Picrotoxin mg.	Amphetamine mg.	Caffeine gm.	Apex Rate	Arrhythmias
1	3.0	II	24	0	150	3.5	140	Auricular tachycardia.
2	?	III	50	69	425	9.0	140	Auricular tachycardia and VPC's.
3	5.0	IV	72	484	350	14.0	145	Auricular tachycardia and VPC's given procaine.
4	3.4	IV	18	513	120	2.5	144	Auricular tachycardia.
5	2.0	III	27	297	0	1.0	120	Coupling on picrotoxin. Given IV quinidine.
6	1.5	II	18	12	125	2.5	92	Coupling. Given procaine.
7	4.8	IV	30	60	130	8.5	140	Coupling.
8	2.5	IV	32	0	25	0.5	80	PVC's on admission. Analeptics stopped.
9	2.0	III	8	41	75	1.5	96	PVC's.
10	1.8	III	24	400	75	1.5	170	Auricular tachycardia.
11	5.4	III	96	423	500	10.5	140	Auricular fibrillation.
12	5.0	II	36	457	450	8.5	110	Many PVC's after picrotoxin.
13	4.8	III	72	840	373	3.5	140	Auricular tachycardia.
14	2.0 + 12.0 gm. chloral	III	48	0	35	1.0	100	Many PVC's.

contractions after several doses of picrotoxin, and showed transient prolongation of the QT interval in addition. This is the only case of electrocardiographic changes produced by picrotoxin that we observed other than the arrhythmia mentioned above.

Picrotoxin convulsions were produced in seven cases but in only one was intravenous pentothal required to control the convulsion. In six cases the fall in blood pressure did not respond to analeptics and oxygen, and neosynephrine was given, with good results in four. Two cases were given blood transfusions to combat shock.

Pneumonia developed in 11 cases but in no case was it severe, and recovery was uncomplicated. Five cases aspirated gastric contents and were bronchoscoped.

Seven cases developed laryngospasm and four were intubated. One required tracheotomy. Ten additional cases were given an intratracheal airway.

Three cases had such severe respiratory depression that a respirator had to be used. Two recovered; the third, a 77 year old diabetic woman, died after 12 hours in the hospital.

Two cases developed lower nephron nephrosis from prolonged shock and renal ischemia:

The first was a 37 year old woman who had taken 5.0 gm. Seconal eight hours before admission. She entered in group IV with profound shock and respiratory paralysis. In addition to the usual measures, she was given artificial respiration until the respirator was available. She responded well and after three days regained consciousness, but in the interim she had developed a typical lower nephron nephrosis with complete anuria. This was treated by fluid and salt restriction and with BAL because of the possibility (later excluded) of mercury ingestion. She also recovered from the nephrosis, and follow-up examination five months later showed no detectable impairment of renal or cerebral function.

The second was a 50 year old woman who took 1.8 gm. of phenobarbital eight hours before admission and entered in shock. Blood pressure was 80/50 mm. of Hg. Initial urine showed 3 plus albuminuria. She was treated in the usual manner but her shock persisted despite transfusions and neo-synephrine, and she developed anuria 12 hours after admission. She died 24 hours after admission.

Two cases died with hyperthermia:

The first was a 44 year old woman with multiple sclerosis who took 2.5 gm. of Seconal two hours before admission and entered in group II with a normal temperature. Over the next two days her temperature rose to 106° and on the third day it rose to 108° despite ice packs. She died in hyperthermia. At autopsy there was no infection or cerebral hemorrhage.

The second was a 57 year old woman with arteriosclerotic heart disease who took an unknown amount of Seconal one to two hours before admission and entered in group III. Her response to treatment was poor, and she developed a marked temperature rise and died after 24 hours in the hospital with a temperature of 107°. Autopsy showed no infection or cerebral hemorrhage. Large amounts of Seconal were found in the tissues.

We ascribe these deaths to disturbances of the heat regulating center, probably due to the drug, but the effect of prolonged anoxia prior to admission cannot be ruled out. Both of these patients had been given oxygen during their entire hospitalization.

The dangers of excessive fluid are illustrated by the following case:

A 66 year old woman with hypertensive heart disease took 2 gm. Phanodorn six hours before admission and entered in group IV. Except for her fluids she was treated in the usual manner and responded well, but on the third day she went into pulmonary edema complicated by pneumonia. She had received 10 L. of fluid during the first 48 hours by mistake.

Thus, of five deaths only one was brought about primarily by respiratory depression, and this patient was a 77 year old diabetic.

Summary

1. A physiologic system of classification of the severity of the coma of barbiturate poisoning has been presented and applied to analysis of a series of 300 cases.

2. On the basis of an analysis of 209 cases treated prior to July, 1949, it has been shown that caffeine and amphetamine may cause fatal arrhythmias when given in doses exceeding 6 gm. and 300 mg. per 24 hours, respectively.

3. A rational program of treatment based on the classification of the severity of coma has been presented, and the results of the application of this system to a series of 91 patients treated after July, 1949, discussed. No serious arrhythmias were observed. Picrotoxin caused premature ventricular contractions in two cases.

4. The most serious complications in our experience have been lower nephron nephrosis and hyperthermia. Secondary pneumonia has not been a serious problem.

5. The mortality rate in the 209 cases treated without a standard program of therapy was 13.4 per cent, and in the 91 cases treated with a standard program the mortality rate was 5.5 per cent.

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PRIMARY MALIGNANT DISEASE OF THE LIVER*

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SOME years ago, interest in primary malignant disease of the liver was stimulated by finding at necropsy a few cases in which the correct diagnosis had not been made clinically. A review of the records of patients with this disease in the John Gaston Hospital was undertaken with a hope that common factors might be found that would enable one to make the diagnosis clinically in a higher percentage of cases. With the advent of the war, this work was interrupted and has only recently been resumed.

Similar studies have been carried out by others. Strong and Pitts [1] reported 55 cases occurring in Vancouver General Hospital from 1920 to 1944. A majority of their cases were in Chinese and Japanese. It is well known that primary cancer of the liver is more frequent among Orientals than among the white race. They emphasized cirrhosis as an etiologic factor, and reported it to be present in 87.2 per cent of their cases.

Smith [2] reported 25 cases and made an effort to determine whether a preëxisting cirrhosis was present or whether the fibrous tissue which was observed was a result of, rather than a precursor of, malignancy. Contrary to the observations of Strong and Pitts, Smith found a preëxisting cirrhosis in 39 per cent of his cases. It was his opinion that cirrhosis as a predisposing factor may have been overemphasized.

Gustafson [3] reported 62 cases occurring in Bellevue Hospital, discovered in the performance of 24,400 necropsies. This gives an incidence of 0.25 per cent, which is probably somewhat lower than the incidence found by other writers. In those cases cirrhosis was present in 64.1 per cent of the liver cell variety and in 33.3 per cent of the cholangioma group.

Gustafson quoted the diagnostic criteria of Symmers, which are as follows: (1) male over 35 years of age; (2) a large tumor mass in the right lobe of the liver; (3) no discoverable tumor elsewhere; (4) jaundice, usually mild; (5) ascites; and (6) an unexplained low grade elevation of temperature.

Tull,[4] a British government pathologist in Singapore, reported 134 cases occurring in 17,664 autopsies. This gave an incidence of 0.76 per cent which, for the Orient, is rather surprisingly low. It has been pointed out, however, that the incidence of primary cancer of the liver varies in different provinces of the Orient. Tull was impressed with the short duration of the disease. The average stay of those patients in the hospital prior to death was two weeks. All of them dated the onset of symptoms as less

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than one month prior to admission. Of Tull's 134 patients, pain was the presenting symptom in only 12 cases. This is astonishing, since it is in such marked contrast to the experience of others. Perhaps it may be explainable, in part at least, on the basis of a higher threshold for pain among the Orientals.

The present series consists of 38 proved cases of primary cancer of the liver occurring from 1920 through 1951. A number of additional cases were excluded because there might be some slight doubt as to the accuracy of the diagnosis. The diagnosis was established by necropsy in 34 of the 38 cases. Brief reference will be made later to the four that did not come to postmortem examination.

Thirty-four of these patients were males and four were females. Fifteen were white and 23 were Negroes. At first glance, this would seem to indicate that the incidence is higher in the Negro race, but since there are four times as many Negroes as whites admitted to the John Gaston Hospital, our experience would indicate that there is a statistically important predominance of primary malignant disease of the liver in the white race. The average age on admission to the hospital was 57 years. The oldest patient was 78 and the youngest 26 years of age. This age incidence corresponds rather well to that reported in other series. It should be borne in mind, however, that there are instances on record of the occurrences of the disease in early life.

The most frequent presenting symptom in this series was pain. It was present in 27 of the 38 cases. With the exception of Tull's Singapore series, all others have reported pain as the chief complaint in a high percentage of instances. Strong et al. found it in 30 of 55 cases, Gustafson in 19 of 22 cases, Counseller and McIndoe [5] in four of five patients. Lewis,[6] in his discussion of pain in acute and chronic diseases of the liver, states that pain is an outstanding symptom in both hepatoma and cholangioma. He says further that it often is the first symptom and may be very severe. The location of the pain, as was observed in this series, is most often in the right upper quadrant or epigastrium, with frequent radiation to back or shoulder. Lewis mentions that the location may be at the site of radiation before it becomes localized to the region of the liver. He ascribes the sudden exacerbation of pain which occurs in many instances as frequently being due to hemorrhage into a necrotic cavity.

In seven instances the patients themselves had discovered an abdominal mass and presented themselves for diagnostic study on this account. Nine of the series complained principally of vague and indefinite digestive disturbances. Abdominal swelling, usually due to ascites, was the principal complaint in eight.

In 33 cases in which the date of onset of symptoms could be ascertained with a reasonable degree of accuracy, the average duration was 8.3 months. The shortest was five days and the longest, six years.

Objectively, an enlarged liver was reported in 33 cases. In the five cases in which the liver was not enlarged, advanced Laennec's cirrhosis was present. The enlarged livers were irregular in contour or nodular in 26. They were smooth in four instances and in three it was not stated. Many of the enlarged livers were tender. Splenomegaly was present in three instances, in two of which rather advanced cirrhosis was present.

Ascites was detected clinically in 22. At least a small amount of fluid, often bloody, was found at necropsy in most of the remaining cases. Jaundice, of the obstructive type, was present in 23 cases.

In this series the malignancy was of the liver cell type, or hepatoma, in 35 instances, and of the intrahepatic bile duct cell type, or cholangioma, in only three. While it is well known that hepatoma is more frequent than cholangioma, the comparative incidence of the latter in this series is for some unknown reason unusually low. Bockus [7] gives the ratio of hepatoma to cholangioma as about two to one. This seems to be the experience of other investigators.

The pathologists found a preëxisting Laennec's cirrhosis in 20 of these 38 cases. Attention has already been called to the divergence of opinion relative to the importance of Laennec's cirrhosis as an etiologic factor in hepatic carcinoma. It should be emphasized, as illustrated by this series and others, that the absence of preëxisting portal cirrhosis by no means rules out the diagnosis of primary carcinoma of the liver. One feels more confident in making the diagnosis, however, if he can demonstrate evidence of preëxisting cirrhosis.

Two of these cases were victims of two independent malignant tumors. In addition to hepatoma, one had carcinoma of the rectosigmoid and the other, carcinoma of the prostate.

It was rather amazing that in 34 cases in which the information was available, a severe grade of anemia was present in only 12. A red cell count of 3.5 million was arbitrarily selected as the dividing line between normal and anemia. This series seems to indicate that primary cancer of the liver is not so prone to be associated with anemia as comparable malignant disease of other organs. The reason for this is by no means apparent.

Metastasis to other organs was demonstrated in 24 cases. This represents 70.6 per cent of the 34 cases that came to necropsy. This is probably a little higher incidence than has occurred in the other series reported. Numerous investigators have commented on the infrequency of extrahepatic metastasis of hepatic cancer as compared to malignant disease of other organs. It has been shown, further, that when metastasis occurs it is relatively late.

The lungs were by far the most frequent site of metastasis. In 18 of the 24 cases the lungs were secondarily involved. The regional or mediastinal lymph nodes came next in frequency and were found in nine cases. In two cases metastasis occurred to the periumbilical region of the abdominal wall, and in these two no other metastases were discovered. In one case

metastatic lesions were demonstrated in both suprarenal glands, and in two other cases the right suprarenal was involved. Other locations of occasional metastasis were the pancreas, peritoneum, pleura, rib, diaphragm, omentum, jejunum and capsule of the spleen. In one case there was extension of the malignant growth into the inferior vena cava, producing malignant thrombosis, and in one other case it had extended into the inferior vena cava and also the right auricle.

The immediate cause of death was exsanguination in nine cases. In four of these, rupture of esophageal varices was demonstrated, and in five there was hemorrhage into the peritoneal cavity. In one of the latter there was rupture of the portal vein, and in one other, rupture of the liver.

A few of the cases in this series are of sufficient interest for one reason or another to justify reporting briefly. The first case will probably be reported elsewhere in detail by Dr. William T. Tyson, a member of our Surgical Staff, but it is sufficiently unusual to justify a reference in this discussion also.

Case Reports

Case 1. R. W., a Negro male 45 years of age, was admitted to the medical ward of the John Gaston Hospital October 23, 1948, because of shock and abdominal pain. The following history was obtained. About eight hours before admission, while picking cotton, he was seized with a very severe pain at the top of the right shoulder. During the next 20 minutes the pain moved down the right anterior chest into the right paraumbilical region, where it remained and continued to be very severe. Vomiting occurred a few times, but the vomitus did not contain blood and was not particularly remarkable. Intravenous fluids, blood and plasma were administered during the next two hours, with some improvement and a rise in blood pressure from 70/60 to 105/65 mm. of Hg. During the next eight hours definite abdominal rigidity and rebound tenderness developed. Surgical consultation was obtained and laparotomy was advised and performed. At operation, the peritoneal cavity was found to contain an estimated 2,000 c.c. of blood. A ruptured cystic structure about 2 cm. in diameter, which bled profusely when touched, was found on the anterosuperior surface of the right lobe of the liver. A biopsy was obtained and the rupture in the liver repaired. His postoperative recovery was prompt and he was discharged from the hospital November 8. The pathologic diagnosis of the tissue removed was hepatoma.

He was re-admitted to the Hospital several times. In March, 1950, he was admitted with a tumor nodule in the abdominal wall. This tumor nodule was removed for microscopic study, and the pathologic diagnosis was primary liver cell carcinoma, metastatic to abdominal wall. His last admission was July 14, 1950, and unfortunately he was discharged from the hospital July 31, 1950, and died at home three days later. This was one of the four cases that did not come to necropsy.

Comment: While rupture of the liver is not extremely rare in primary cancer of the liver, it is usually discovered at the autopsy table. This case is somewhat interesting and unusual in that he recovered postoperatively from this massive hemorrhage and survived for over 21 months.

Case 2. C. L. L., a Negro female 32 years old, was first admitted February 21, 1945, with the chief complaint of an abdominal mass which she had first noticed two years previously. The mass had gradually and progressively increased in size. Examination disclosed an epigastric mass, about the size of a grapefruit, slightly movable

and descending on inspiration. After the patient had convalesced from pneumonia which she developed while in the hospital, laparotomy was performed on March 31 and a globular mass measuring 13 by 10 by 6 cm. was removed from the ventral and inferior surface of the right and left lobes of the liver. Postoperative convalescence was satisfactory, and she was discharged from the hospital April 19, 1945. The pathologist's report on the mass removed was hepatoma.

Her next admission to the hospital was March 31, 1949, exactly four years after the operation. She stated that she had been entirely well until approximately three months prior to the second admission, at which time she began to lose weight and noticed a slightly yellowish tint to the sclerae. During that three month period she lost 60 pounds in weight and became quite weak, and the jaundice increased in intensity. In addition to the intense icterus, examination revealed that the liver was enlarged down to the crest of the ilium and was rather tender and extremely firm. No evidence of ascites was present. On this admission a punch biopsy of the liver was performed and this, too, was diagnosed hepatoma. She was discharged April 25, 1949, and Social Service follow-up revealed that she died in Chicago during the summer of 1949. This constitutes the second of the four cases in this series in which necropsy was not performed. These specimens have just been restudied by Dr. Russell S. Jones, in our Department of Pathology, who states that there is no doubt about the correctness of the diagnosis.

Comment and Discussion: This case presents a number of features which are remarkable. Hepatoma is uncommon in women. It is uncommon under the age of 40 and, in our experience at least, is less common in the Negro race than in the white. The duration of the disease is astonishing. From the history, we have to assume that the cancer was present for a two year period prior to operation and, to our certain knowledge, she lived over four years after operation. Cancer of the liver is usually thought of as a rapidly fatal disease but, as this case so well illustrates, there are exceptions. This case illustrates, also, the slowness with which cancer of the liver metastasizes to other structures. It is also an example of the benefits which may be derived from surgical treatment in some of these cases.

Removal of tumors from the liver is not an innovation in surgery. As far back as 1899, W. W. Keen [8] reported removal of a hepatoma measuring 14 by 11 by 7.5 cm. from the left lobe of the liver and referred to two cases which he had previously reported, all successful. In addition, he tabulated 76 cases of resection of the liver for hepatic tumors done prior to that time by various surgeons. Wallace [9] reported a case in which a large hepatoma was removed from the right lobe of the liver, and a five year follow-up showed the patient to be well, with no signs of recurrence. He emphasized the importance of the removal of normal liver tissue around the entire circumference of the tumor mass. He stated that the tumor had been present for at least four years at the time of operation. Yeomans [10] in 1915 reported a case upon which he performed a second operation for a recurring cancer of the liver more than seven years after the primary operation. Charache [11] in 1939 reported a case, made a complete review of the literature up to that time, and advocated more active and frequent surgical intervention in carcinoma of the liver.

Case 3. B. J., a Negro male 63 years of age, was admitted December 23, 1940, complaining of pain and soreness in the right upper quadrant of the abdomen, with swelling of the abdomen and fever of 10 days' duration. Examination of the abdomen revealed a large, hard, tender liver with what was thought to be some irregularity of contour. Liver flatness was found to extend upward to the fourth rib anteriorly and to the sixth rib in the anterior axillary line, and the right diaphragm was thought to be elevated about three inches posteriorly. This was confirmed by roentgenologic examination. The visiting staff physician thought that there was an area of fluctuation about 5 cm. in diameter on the anterior surface of the right lobe. There was a daily elevation of temperature, as high on occasions as 102° F. Blood count revealed 22,400 leukocytes, 95 per cent of which were granulocytes.

Laparotomy was performed on December 31, with a preoperative diagnosis of liver abscess. When the abdomen was opened the liver was found to be approximately twice normal in size and studded throughout with large and small isolated and confluent grayish nodules. Both lobes were involved. A biopsy was obtained and the abdomen closed without further surgical procedure. The pathologic diagnosis was hepatoma. The patient was discharged from the hospital January 9, 1941, and follow-up revealed that he died at home on January 20, 1941.

Comment: This is another of the four cases included in this series in which necropsy was not performed. It is reported largely for that reason, but it also illustrates quite well a problem in differential diagnosis which is not infrequent in primary cancer of the liver. It, too, is an example of the rapidity with which many of these cases progress to a fatal termination.

Case 4. H. T., a 71 year old Negro male, was admitted to the hospital May 3, 1951, complaining of vague and indefinite digestive disturbances, pain and soreness in the upper abdomen, a sense of abdominal fullness and constipation of approximately one year's duration. Examination revealed the abdomen to be enlarged and to contain a large, hard, moderately tender mass in the upper right and middle abdomen which the examiner estimated to be approximately the size of a basketball. The patient was not jaundiced, but the examiner thought that a small amount of ascitic fluid was present. Laboratory investigations were not particularly revealing. Roentgenologic studies showed no evidence of malignancy in other organs. A tentative diagnosis of primary cancer of the liver was made and a punch biopsy was performed on May 11. The consensus of the pathologists was that it presented a hepatoma but, for confirmation, they suggested that another biopsy be performed. This was done 10 days later, and the pathologists were convinced of the correctness of the diagnosis. The patient was discharged from the hospital May 24, 1951. It was learned through Social Service follow-up that he died on July 14, 1951.

Comment: This is the fourth case in this series in which the diagnosis was not confirmed at necropsy. The hazard of basing a diagnosis of primary cancer of the liver on punch biopsy will be discussed later, but if the clinical picture had not been so typical in this case and if two positive biopsies had not been obtained, this case would have been excluded. Dr. Russell S. Jones has recently restudied these specimens and has confirmed the diagnosis of hepatoma.

Case 5. B. T., Negro male 56 years of age, was admitted to the hospital October 31, 1950, complaining of abdominal pain, distention of the abdomen and shortness of breath of 10 weeks' duration. Prior to that time he had been asymptomatic. The

first symptom noted was pain in the right lower chest and in the right upper quadrant of the abdomen. He was told by a private physician at that time that his liver was enlarged. All his symptoms became progressively worse until the time of admission. Examination disclosed elevation of the right diaphragm. The abdomen was greatly distended and the liver could be palpated 6 cm. below the right costal margin. It was irregular, hard and tender. A large amount of ascitic fluid was present. Pitting edema of the ankles was described as being very slight by both the examiner and the pathologist at necropsy. No jaundice was present. Numerous paracenteses were done with some symptomatic relief, but the patient's condition progressed downward very rapidly and he died November 11, 1950. The pathologic diagnosis at necropsy was (1) cirrhosis of the liver; (2) hepatoma; (3) growth of the hepatoma into the inferior vena cava; (4) metastasis to the lung; (5) pulmonary embolus of tumor tissue. The following is a partial quotation from the pathologist's discussion: "This 56 year old man had cirrhosis of the liver and hepatoma. Growth through the central veins into the inferior vena cava had occurred. Metastatic spread was present in the lung. Death was probably the result of an embolus of a large piece of tumor tissue."

Case 6. Mrs. A. W., a 68 year old white married female, was admitted to the hospital June 6, 1950, in shock and comatose. This patient died a few hours after admission, so that adequate studies were impossible. The meager history obtained from a relative indicated that the patient had been seized suddenly with a severe substernal pain which radiated to both shoulders and both arms about 16 hours prior to admission. Examination disclosed a systolic murmur over the region of the apex. The patient was not jaundiced. Ascites was not present. The liver was not enlarged, and both the examiner and the pathologist noted that there was no edema of the lower extremities. At necropsy there were found hepatic cell carcinoma, invasion of the hepatic veins, extension into the inferior vena cava and right auricle, and embolism of the left pulmonary artery without pulmonary infarction.

Comment: Cases 5 and 6 are reported because of the rarity of invasion of the inferior vena cava and right auricle by tumor tissue. In 1924 Simpson [12] reported four cases and, at that time, was able to find only 78 cases reported in the literature. Of these 78, only seven were secondary to primary cancer of the liver. In 1939 Gregory [13] reported one case, and his search of the literature revealed only 11 previously reported cases due to primary cancer of the liver. Gregory mentioned dilated superficial veins on the anterolateral portions of the thorax and abdomen as important diagnostic criteria if present, but added that they are absent in half or more of the cases. They were not present in either of the cases in this series. He also mentioned the significance of edema of the lower extremities occurring as an early, and often the first, symptom. Oddly enough, that was absent also, or very slight, in both these cases. No attempt has been made in this study to determine the number of cases reported in the literature since 1939.

The inadequacy of the punch biopsy in establishing the diagnosis of primary malignant disease of the liver is illustrated by two cases (B. W. and E. F. M.). In the former, pathologists reported adenocarcinoma, primary site undetermined, and in the second, metastatic carcinoma of the liver, the primary site probably the bronchus. Both these cases came to necropsy and were found to have primary cancer of the liver (hepatoma). The likelihood

of aspirating normal liver tissue which is obtained between malignant nodules is considerable. Furthermore, the amount of tissue ordinarily obtainable is so small that the pathologist is placed at a decided disadvantage.

Laparotomy is by far the best means available of confirming ante mortem the diagnosis of primary cancer of the liver, and it affords the patient his only hope of having his life prolonged if a resectable tumor is discovered. It seems reasonable that, unless there are definite contraindications, every patient in whom primary cancer of the liver is strongly suspected should have the benefit of an exploratory laparotomy.

Roentgenologic study is of great value in establishing a diagnosis of primary malignant disease of the liver. Strong et al., in their Vancouver series, emphasized elevation and limitation of motion of the right diaphragm. In that connection, a plea should be made that roentgen-ray be used merely to confirm the finding which had previously been determined by percussion. If the left lobe is involved, Aub's sign may prove helpful. This sign consists of percussing downward over the left chest posteriorly near the spine until liver flatness is reached. At this point, percuss horizontally to the left until the note becomes resonant. Normally this does not exceed 5 cm. in distance from the midline. In tumors involving the left lobe, it may be as much as 8 or 9 cm. Adams,[14] in reporting a case of hepatoma of the left lobe which he removed and in which the preoperative diagnosis was incorrect, commented in retrospect that if he had paid more attention to the displacement of the gas bubble in the stomach to the right and downward on the roentgenogram, the chances of making a correct preoperative diagnosis would have been enhanced.

Schatzki [15] reported a case of carcinoma of the left lobe of the liver which was diagnosed by roentgen-ray alone. The criteria upon which he based this diagnosis were (1) metastatic areas in the lungs, (2) enlargement of the left lobe of the liver, (3) the right lobe apparently smaller than normal, (4) esophageal varices, (5) stomach displaced to the left, duodenum to the right. He hastened to add that a diagnosis by roentgen examination alone is not possible unless cirrhosis also is present. While he did not say so, his security in making that diagnosis was probably enhanced by the findings of Lisa, Solomon and Gordon [16] and others that malignant disease of other organs very rarely metastasizes to a cirrhotic liver.

Schatzki also mentioned elevation and limitation of motion of the right diaphragm and stated that a localized area of bulging could be demonstrated frequently.

Summary

1. The records are reviewed of 38 cases of primary malignant disease of the liver occurring in the John Gaston Hospital from 1920 through 1951.

2. Cases reported include two in which the hepatoma had extended into the inferior vena cava, and in one of these also into the right atrium.

3. The diagnosis of primary malignant disease of the liver is discussed.

Conclusions

1. An enlarged, hard, painful, tender, irregular or nodular liver, with or without ascites and with or without jaundice, should always make one think of primary malignant disease. If present in a male 40 years or more of age, the possibility is greater.

2. In a patient presenting the above findings, if a diagnosis of preëxisting cirrhosis can be established one can be almost certain of primary hepatic cancer.

3. Laparotomy is by far the best method of confirming the diagnosis.

4. Resection of the tumor mass, when possible, may be expected to prolong appreciably the patient's life.

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RECENT ADVANCES IN THE PATHOGENESIS AND TREATMENT OF ATHEROSCLEROSIS*†

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ATHEROSCLEROSIS is one form of arteriosclerosis. Arteriosclerosis is a condition involving thickening of the arterial wall, accumulation of lipid substances, and degenerative changes with calcium deposition, distortion and loss of elasticity. There are generally considered to be several varieties or forms of arteriosclerosis. Atherosclerosis is the term applied to the thickening of the intima by plaque formation resulting from the deposition of cholesterol and lipids and the laying down of new connective tissue. Atherosclerosis involves especially the large conducting, elastic arteries, such as the aorta, but also smaller arteries, such as the coronaries and the cerebrals. Medial or Mönckeberg's sclerosis involves degenerative and destructive changes in the media, with deposition of fatty substances and calcium salts. It is more often found in medium sized, muscular arteries, such as the femoral. Diffuse, hyperplastic arteriolosclerosis occurs in the smallest arteries and arterioles, and involves a thickening of the wall and narrowing of the lumen due to an increase in the amount of connective tissue in the intima and media, with hyaline degeneration and elastic hyperplasia. Arteriolosclerosis may be widespread but is most frequently found in the spleen, pancreas, kidney and adrenal. Most likely these forms of arteriosclerosis are manifestations of the same fundamental pathophysiologic process, and not infrequently they occur in the same individual. Twenty years ago the concept prevailed that arteriosclerosis was an inevitable part of the aging process. This false doctrine played an important part in discouraging research in the field. It is true, of course, that from the time of birth there is a very slow, gradual replacement of elastic and smooth muscle tissue in the arterial tree by connective tissue, so that the arteries of even a 10 year old are less elastic than they were at the age of five, but the term hyperplastic or senile arteriosclerosis should not be applied to this process unless it is excessive. Here, as is true in many other fields of medicine, it is difficult to draw a dividing line between the normal and the abnormal.

From a clinical standpoint, atherosclerosis is by far the most important form of arteriosclerosis. It is the lipid-laden intimal plaque which narrows the lumen of the coronary, cerebral, renal and other arteries and thereby reduces the blood supply and produces dysfunction of the heart, brain, kidney

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and other tissues, frequently leading to invalidism and death. In the Western world, atherosclerosis is now the "Captain of the Men of Death" and, in collaboration with hypertension, with which it is frequently associated, is responsible for almost one-half of the present yearly mortality in the United States. Moreover, morbidity and mortality from atherosclerosis are increasing as the life span is lengthened and the proportion of our population over 40 continues to grow.

Pathophysiology of Atherosclerosis

In atherosclerosis the elasticity of the involved arteries is decreased and the arterial pulse wave travels more rapidly over the arterial tree. The decreased elasticity also tends to increase the systolic and decrease the diastolic pressure. Ordinarily, the diastolic pressure does not fall, probably due to accompanying arteriolosclerosis, which delays the run-off of blood into the capillary bed. Not uncommonly, however, the systolic and pulse pressures are raised in atherosclerosis. The Korotkov sounds are somewhat higher pitched over an arteriosclerotic artery than over a normally elastic one. As previously mentioned, the narrowing of arterial lumina by atheromatous plaques produces a decrease in the blood supply to various organs and tissues, and an even more severe decrease results from thrombotic occlusion of an atheromatous artery. The resulting clinical syndromes include cardiac insufficiency, cerebral and other nervous manifestations, intermittent claudication, renal dysfunction, diabetes mellitus and gastrointestinal disturbances.

Pathogenesis of Atherosclerosis

Recent studies have confirmed the facts that atherosclerosis appears more frequently in certain families and in stocky, pyknic, overweight individuals. Indeed, the children of families with a history of atherosclerosis have at least twice as much likelihood of developing clinical atherosclerosis as those of families with no history of atherosclerosis.[1] Heredity and body type, however, must operate through pathophysiologic mechanisms which present and future research must determine. Although the pathogenesis of clinical atherosclerosis is still unsettled, recent research on pathogenesis has contributed much to our knowledge and has involved seven approaches, viz., diet, cholesterol and lipid metabolism, endocrines, sex, hypertension, local factors and experimental atherosclerosis.

(A) *Diet:* There is much evidence that the incidence and severity of atherosclerosis among populations of the world vary significantly and are correlated with differences in the economically and culturally conditioned patterns of diet and nutrition. Atherosclerosis is much more prevalent among peoples of the Western world, whose dietary includes considerable amounts of cholesterol and fat, than among those whose dietary is low in these constituents. Thus a low incidence of atherosclerosis has been re-

ported in Chinese, Okinawans, Japanese and African Negroes of the 40 to 70 age group. Interestingly, there is little atherosclerosis among the native Ceylonese, whose dietary is low in cholesterol, fat, protein and calories, whereas among the British and Dutch colonials of Ceylon, whose dietary is similar to that of their homelands, the incidence of atherosclerosis in the same older age groups is high.[2] Moreover, the incidence of death and disability from atherosclerosis, including coronary disease, decreased in a number of European countries during World Wars I and II when there was a sharp reduction in the amount of cholesterol and fat in the diet. Particularly accurate statistics are available for Norway,[3] Sweden, and Finland during World War II. Overnutrition and obesity are generally associated with increased atherosclerosis, whereas undernutrition and wasting disease are associated with decreased atherosclerosis. However, high calorie diets are apt to be rich in cholesterol and fat, whereas low calorie diets are usually low in these constituents. That the cholesterol content may be more important than the fat content is suggested by the fact that Eskimos, who have a high animal fat diet but low to moderate cholesterol intake, show a low incidence of atherosclerosis.

(B) *Cholesterol and Lipid Metabolism:* That cholesterol and lipid metabolism is related to atherogenesis is suggested by the fact that certain clinical conditions frequently showing hypercholesterolemia and hyperlipemia are characterized by a relatively high incidence and severity of atherosclerosis. Such conditions include diabetes mellitus, hypothyroidism, familial hypercholesterolemia, xanthomatosis, nephrosis and biliary obstruction. Although some patients with atherosclerosis show plasma total cholesterol values within the normal range (100 to 275 mg. per cent), the average is higher for patients with atherosclerosis as compared with normals of the same age groups. Moreover, many more patients with atherosclerosis show plasma cholesterol values above the normal than do presumed non-atherosclerotic individuals. It is possible, but by no means proved, that all patients with atherosclerosis show an increased plasma cholesterol in terms of the presumed normal level for the given individual. Moreover, the cholesterol/phospholipid ratio is increased in most patients with atherosclerosis, with a resulting decreased solubilizing effect on cholesterol. There is also inconclusive evidence that the proportion of cholesterol in the form of cholesterol esters is increased in clinical atherosclerosis.[4]

In recent years it has been increasingly recognized that plasma cholesterol exists in a state of colloidal solution in molecules and molecular aggregates in combination with phospholipids, fatty acids and proteins. There is some evidence that the proportion of beta-lipoproteins relative to alpha-lipoproteins is increased in the plasma in atherosclerosis,[5] the molar ratios of cholesterol to phospholipid being 2 : 1 in beta-lipoprotein and 1 : 1 in alpha-lipoprotein. One research group believes that the development of atherosclerosis is related to the large particle size of newly absorbed lipids (chylo-

microns) appearing in the plasma and to the height and duration of the chylomicronemia following fat-rich meals.[6] During the past two years great interest has centered about the work of Gofman and his colleagues, who have reported that the plasma of human atherosclerosis shows an increased concentration of certain lipoprotein macromolecules of comparatively low density.[7] These are referred to as S_f 10–20 class lipoproteins. There is evidence of impaired ability in atherosclerosis to degrade these lipoproteins into smaller ones of the S_f 3–8 class. However, the causal relationship of these comparatively large, low density lipoprotein molecules to atherosclerosis remains to be demonstrated. Keys, after statistical analysis of Gofman's data, contends that the correlation between plasma cholesterol and atherosclerosis is as good as the correlation between the plasma S_f 10–20 lipoproteins and atherosclerosis.[8] This is denied by Gofman. Obviously further work is necessary, and the United States Public Health Service is presently subsidizing several ultracentrifuge laboratories in the collection of data which should settle this important question and further clarify the pathogenesis of atherosclerosis.

(C) *Endocrines:* As stated previously, diabetes mellitus and hypothyroidism frequently show increased cholesterolemia and atherosclerosis. Moreover, there is a high incidence of atherosclerosis in patients with hyperfunction of the adrenal cortex (e.g., Cushing's syndrome), and prolonged cortisone therapy produces increased plasma cholesterol levels. The importance of the adrenal cortex in cholesterol metabolism is further shown by its high content in cholesterol, as well as by the ability of the gland to synthesize, store and discharge cholesterol.

(D) *Sex:* The incidence of atherosclerosis is considerably higher in males than in females under 40, but is similar for the various parts of the arterial tree after 40, with the exception of the coronary arteries. The explanation of the 4:1 ratio of the incidence of coronary atherosclerosis in males as compared with females is part of the broader problem of the pathogenesis of atherosclerosis. The most promising lead to date is the finding of Dock that the intima of the coronary arteries is considerably thicker in the male, and that this difference is present from birth.[9]

(E) *Hypertension:* There is good clinical and pathologic evidence that hypertension accelerates the onset and accentuates the progress of atherosclerosis. Atherosclerosis of the aorta is most pronounced in the abdominal region, where the pressure, particularly in the standing position, is higher. Atherosclerosis in the pulmonary arterial tree is found only in the presence of pulmonary hypertension. It should be remembered, however, that hypertension of long standing may occur without atherosclerosis, and that extensive atherosclerosis may occur in the presence of normotension. Indeed, recent vital statistics show that 40 per cent of atherosclerotics are hypertensive and 60 per cent of hypertensives are atherosclerotic. Obviously, hyper-

tension is an auxiliary but not a basic pathogenetic mechanism in atherosclerosis.

(F) *Local Factors:* Even though atherosclerosis may ultimately be proved pathogenetically to be based on altered cholesterol and lipid metabolism, it is obvious that local factors are important, since atheroma formation is not general but focal. Local areas of increased permeability may result, for example, from infections of the arterial wall. Likewise, lipoid deposition may be increased by local hydrodynamic effects, as seen in the atheromatous plaques at the origin of the intercostal and lumbar arteries. Experiments involving the filtration of serum through excised arteries, as well as intravascular injections of colloidal cholesterol solutions, suggest that cholesterol and lipids are filtered through the intimal mucosa rather than brought to the media and intima by the vasa vasorum. Lansing and his colleagues believe that the basic lesion of atherosclerosis is a localized fibrocalcific change in the media, with subsequent cholesterol and lipid accumulation in the overlying thickened intima.[10]

(G) *Experimental Atherosclerosis:* The reproduction of a given human disease in the experimental animal has frequently led to increased knowledge and more effective treatment. Atherosclerosis does not occur to any significant extent in the ordinary laboratory or domestic animals, and indeed is rare among animals of zoölogical gardens. The one exception to this is the chicken, which shows spontaneous atheromata, the histology, biochemistry, gross appearance and distribution of which are similar to atherosclerosis in man. Experimental atherosclerosis was first produced by Anitschkow some 40 years ago by means of cholesterol feeding in rabbits.[11] Experimental cholesterol atherosclerosis in this species is characterized by hypercholesterolemia and hyperlipemia, and by atheromata similar in distribution and appearance to human atherosclerosis except that the aortic lesions are mainly in the thoracic region. The objection that the rabbit is herbivorous was subsequently met a decade ago by the production of experimental cholesterol atherosclerosis in the omnivorous chicken by cholesterol feeding.[12] Later, hypercholesterolemia, hyperlipemia and experimental atherosclerosis were produced in the chicken by stilbestrol. Five years ago experimental cholesterol atherosclerosis was produced in the carnivorous dog by Steiner and Kendall by means of cholesterol-thiouracil feeding.[13] In all known respects, except for the high plasma cholesterol level (approximately 1,000 mg. per cent) and the hepatic cholesterolosis, experimental atherosclerosis in the dog resembles closely human atherosclerosis. Even the definite hypercholesterolemia ordinarily necessary for the production of experimental cholesterol atherosclerosis has been minimized by the administration of small amounts of cholesterol to rabbits and to chickens, with the production of atherosclerosis in the presence of a mild hypercholesterolemia and minimal cholesterolosis and lipoidosis of the liver and other organs. The guinea pig, hamster and rat have proved highly resistant to experimental cholesterol

atherosclerosis. Very recently, one group of investigators has reported the production of experimental atherosclerosis in the monkey by means of a pyridoxine deficient diet,[14] but this work needs clarification and confirmation.

Experimental cholesterol atherosclerosis has been found to resemble human atherosclerosis in many respects. Thus, experimental hypercholesterolemia, hyperlipemia and atherogenesis are enhanced by increased amounts of cholesterol and fat in the diet. Experimental pancreatic diabetes, experimental hypothyroidism and liver damage by carbon tetrachloride have each been shown to enhance experimental atherosclerosis. The cholesterol/phospholipid ratio, the beta-lipoproteins and the S_f 10–20 lipoproteins are increased in the plasma. Cortisone, DCA and ACTH have each been shown to increase the severity of experimental cholesterol atherosclerosis. Hypertension has been shown to enhance the production of experimental atherosclerosis. As first shown by our research group, the increased severity in the hypertensive dog may lead to actual ulceration of atheromatous plaques.[15] Hypercholesterolemia and atheromata are more severe in experimental atherosclerosis of older as compared with younger chickens. Local factors have also been shown to play a rôle in determining the site of experimental atheroma formation. Thus, local injury to the wall of the aorta predisposes this area to subsequent experimental cholesterol atheroma development.[16] Moreover, immobilization of a segment of arterial wall predisposes to experimental atheroma formation in this region.[17] While the many foregoing similarities between experimental cholesterol atherosclerosis and human atherosclerosis are not proof of a common partial pathogenesis, research findings in experimental atherosclerosis point strongly to altered cholesterol and lipid metabolism as an important basic factor in the pathogenesis of clinical atherosclerosis.

Treatment of Atherosclerosis

Evaluation of a therapeutic measure in clinical atherosclerosis is difficult, particularly because the variability and chronicity of the disease make necessary the study of large numbers of patients over a period of years. Hence, experimental cholesterol atherosclerosis is valuable as a tool not only for studies on pathogenesis but also for treatment evaluations under well controlled conditions. It should be emphasized, however, that since the exact relationship between experimental cholesterol atherosclerosis and clinical atherosclerosis still remains to be determined, final evaluations of any new therapy must be made on man. In recent years, a number of therapies have been studied in experimental cholesterol atherosclerosis. Intravenous heparin has been found to influence alimentary lipemia by effecting rapid clearance of plasma lactescence through disruption of lipid-protein bonds, and repeated heparin injections have been shown to decrease experimental cholesterol atherosclerosis. Intravenous injections of such detergents as Triton A-20 not only increase plasma phospholipids and decrease the choles-

terol/phospholipid ratio but also decrease the severity of experimental cholesterol atherosclerosis. Desiccated thyroid has a partial inhibitory effect on experimental cholesterol atherosclerosis,[18] as do lecithin [19] and potassium thiocyanate. Large doses of potassium iodide have an equivocal effect which probably is exerted through altered thyroid function.[20, 21] Further experiments with potassium iodide in experimental atherosclerosis are necessary. Preliminary experiments suggest that estrogens may decrease experimental coronary cholesterol atherosclerosis in the chick but not atherosclerosis elsewhere. There is excellent evidence that the lesions of experimental cholesterol atherosclerosis show marked regression and even complete healing some weeks after cholesterol feeding is stopped.[22, 23] There is also some evidence that chronic undernutrition decreases the severity of the lesions of experimental cholesterol atherosclerosis. Extensive and numerous studies have been made of the effect of the lipotropic substances—choline, inositol and methionine—on experimental cholesterol atherosclerosis. Although there were a few early favorable reports, the evidence is now unequivocal that these lipotropic substances have no therapeutic value in experimental cholesterol atherosclerosis.[24, 25] Although much remains to be learned about the prevention and treatment of experimental cholesterol atherosclerosis, the highly important finding that the atheromatous plaque is reversible has already emerged from this work. There is every reason to believe that human atherosclerosis is likewise a reversible process.

One of the important problems to be solved in relation to the therapy of human atherosclerosis is that of early diagnosis. Atherosclerosis of the retinal arteries may or may not indicate significant atherosclerosis elsewhere, but it is a helpful diagnostic procedure. In view of the frequent involvement of the abdominal aorta in atherosclerosis, an x-ray of the abdomen may reveal calcium deposits in atheromatous plaques. It is important to remember that pipestem radial and tortuous temporal arteries are evidences of medial or Mönckeberg's sclerosis which may or may not be associated with atherosclerosis. Medial sclerosis itself does not significantly narrow the lumen of the artery. Blood chemistry studies in relation to cholesterol, phospholipids, lipids and lipoproteins are of diagnostic value but not conclusive, since there is overlapping of values for non-atherosclerotics and atherosclerotics. Improved methods for the early diagnosis of clinical atherosclerosis are urgently needed.

Recent advances in the treatment of human atherosclerosis, while not decisive, are encouraging. Psychotherapy (by a psychiatrist, if necessary) is of definite value in some patients. This may reduce the chronic stress response of the anterior pituitary and adrenal and thereby delay the process of atherosclerosis. The program of mental and physical activity outlined for patients with atherosclerosis should be individualized and guided by practical, everyday considerations. If nervous tension is present, intermittent courses of the barbiturates may be of value. The vasodilating nitrites,

nitrates and xanthine derivatives are of value in the treatment of angina as a complication of coronary atherosclerosis. The sympathetic blocking drug, Priscoline, appears to have some value in the treatment of intermittent claudication. Lumbar sympathectomy has been of value in some patients with severe atherosclerosis of the lower extremities.[26] If the patient is overweight, a moderate reducing diet should be prescribed. If hypertension is also present, certain of the foregoing measures may reduce the blood pressure and thereby slow the atherosclerotic process.

The favorable results obtained with thyroid in experimental cholesterol atherosclerosis have suggested its use in human atherosclerosis. Obviously, if the patient is also hypothyroid, appropriate amounts of thyroid are indicated. If the patient is euthyroid, the production of chronic hyperthyroidism is obviously not without danger, particularly in patients with coronary atherosclerosis. Accordingly, thyroid medication is not recommended as a general measure for atherosclerosis.

Potassium iodide has been used empirically in the treatment of human atherosclerosis for many years. However, a carefully controlled study with potassium iodide still remains to be carried out. If potassium iodide has any effect in clinical atherosclerosis it is probably through altering thyroid function.

Because of their known physiologic effects and because of early, inaccurate favorable reports in experimental cholesterol atherosclerosis, the lipotropic substances, choline, inositol and methionine, have been widely used in the past few years in the treatment of clinical atherosclerosis. There is presently no satisfactory evidence that these expensive substances have any effect in the prevention or treatment of human atherosclerosis. Instead of their widespread, indiscriminate use, only a large-scale, long-term, well controlled study of their possible value in human atherosclerosis is indicated. Such a study could yield important information relative to atherosclerosis, even though the present view that the lipotropic substances are without anti-atherosclerotic effect should be confirmed.

There is presently much discussion of the use of diets low in cholesterol and fat in the treatment of human atherosclerosis. When continued for periods of six months or longer, such diets cause a decrease in the plasma cholesterol level and in the concentration S_f 10–20 lipoproteins. There is at least one report suggesting, but not proving, that such a diet decreases the incidence of coronary thrombosis recurrence.[27] Clinical experience suggests that severe restriction of cholesterol to less than 0.02 gm. and fat to 5 gm. per day means a difficult, unpalatable diet which is probably no more effective than one containing 0.2 gm. of cholesterol and 25 to 40 gm. of fat. In this connection it should be remembered that, in the face of reduced cholesterol intake, the liver in particular and other tissues increase their synthesis of endogenous cholesterol. Obviously, a long-term, large-scale, well controlled study of low cholesterol, low fat diets in clinical athero-

sclerosis is strongly indicated. Certainly the evidence is presently inadequate to warrant advocacy of any basic changes in the general dietary patterns of population groups showing a high incidence of atherosclerosis. However, a moderate low cholesterol, low fat diet may constitute prophylaxis for individuals with a strong familial history of atherosclerosis.

Conclusions

Atherosclerosis is a disease and not an inevitable consequence of aging. Atherosclerosis is a reversible process. Eventually, more exact knowledge of the causes, pathophysiology, pathogenesis and treatment of atherosclerosis will be obtained through medical and biologic research, inclusive of animal experimentation.

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BAL TREATMENT OF TOXIC REACTIONS TO GOLD: A REVIEW OF THE LITERATURE AND REPORT OF TWO CASES*

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ALTHOUGH the present state of our knowledge concerning gold salts as a therapeutic measure in rheumatoid arthritis is quite incomplete and fundamental questions remain to be answered, many rheumatologists in this country and abroad continue to employ this treatment in selected cases. Investigators who have studied the subject have generally been more impressed with the advantages than disadvantages of chrysotherapy.

At present, the pituitary and adrenal hormones occupy the attention of the medical profession and the general public alike. While the steroid hormones have proved of great benefit to many patients with rheumatoid arthritis, every physician encounters cases in which this form of therapy is not practical. To the average patient, for example, the present cost of therapy is a deterrent. Further, the often rapid reappearance of symptoms following reduction of dosage or cessation of hormone therapy indicates a need for indefinitely continued use, and many physicians as well as patients may prefer to postpone such therapy until further study shall have clarified questions concerning potential advantages or disadvantages of long continued hormone administration. Last, but far from least, a growing number of absolute or relative contraindications to ACTH or cortisone are becoming apparent. For these and other reasons, it will be necessary to depend on the older and more orthodox treatment measures for rheumatoid arthritis, and consequently it is to be expected that gold will continue to be employed in this disease.

It is inevitable that administration of gold salts should provoke a certain incidence of toxic reactions, just as is the case with other heavy metals. Most toxic reactions encountered during the treatment of rheumatoid arthritis with gold salts fortunately prove to be mild and transient. In usual cases, gold reactions disappear promptly when treatment is discontinued, but occasionally, severe, explosive or fulminant reactions occur which may terminate fatally.

Prior to World War II, physicians who encountered gold reactions were at a great disadvantage as there was no specific antidote at their command, and reliance had to be placed on nonspecific measures which had no particular rationale. Repeated publications stressed this unfortunate situation and gave rise to grave feelings of anxiety among those who wished to em-

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ploy gold. The search for antidotes against arsenical poison gases, carried out during the war years, led to a discovery which altered the entire picture. A sulfur-containing compound, 2,3-dimercaptopropanol, known more widely as British anti-lewisite or BAL, was found to be an effective antidote for arsenical gases, and its use was shortly extended to toxicities due to other agents, including gold, with notable success.[1, 2, 3, 4]

In this paper we summarize briefly the literature on this subject and report our own experience in the treatment of two additional cases seriously ill with toxic reactions to gold. We have been able to find in the American, British and Scandinavian literature reports of 50 cases wherein BAL was employed in treatment of gold intoxication. Data given in these reports were not always sufficient to permit an analysis as detailed as might be wished, but were adequate to indicate the general experience with this agent. It should be emphasized that the data presented do not reflect the true incidence of gold toxicity, as only those cases were reviewed in which BAL therapy was utilized. The reported cases were analyzed for information as to the age and sex of the patients, character and severity of the arthritis, amount of gold administered prior to onset of a toxic reaction, and nature of the reactions treated. Information was also sought relative to the interval elapsing between onset of the reaction and institution of BAL therapy, amount and duration of therapy, and finally, the results.

Analysis of Data in the Literature

Age: Patients included in this survey ranged in age from 16 to 67 years. In nine cases the age was not stated. A majority of the patients were in the fifth and sixth decades.

Sex: Data as to sex were available in 42 cases. There were 10 males and 32 females. The preponderance of women probably reflects the higher incidence of rheumatoid arthritis in the female.

Duration of Arthritis: Accurate information as to duration of the arthritis before gold therapy was instituted was available in 21 instances. There was a considerable range in this respect. In one instance, the disease was present for only two months, in another for 20 years. In approximately half the cases, the disease had been present for more than two years at the time gold therapy was initiated.

Type of Gold Compound Administered: In 31 cases, the gold compound was named. There were nine reactions to gold sodium thiomalate (Myochrysine), seven reactions to aurothioglucose (Solganol B Oleosum), six to aurothioglycoanilide (Lauron), four to aurothiogluconate (Myoral), four to gold sodium thiosulfate (Sanochrysine), and one to aurothiosulfate (Aurthion). Because of incomplete data and other variables, such as local availability of a particular product, the incidence of reactions to specific compounds, as reflected in these figures, is probably not significant.

Amount of Gold Administered Prior to Onset of the Toxic Reaction: This factor was difficult to determine with certainty because of variations in methods of reporting cases. Some data on this point were obtainable in 45 cases. It was apparent that toxic reactions to gold resulted from small amounts in some cases and large amounts in others. In one patient, only 20 mg. of gold were sufficient to induce a serious reaction; in another, toxicity did not appear until 7,900 mg. had been administered. On the average, the amount of gold compound administered prior to the onset of a toxic reaction was approximately 1 gm.

Duration of Gold Therapy Prior to the Onset of a Toxic Reaction: The period of time over which gold was administered before the onset of a toxic reaction was stated in 18 cases. The range was one week to seven months; the average duration was 14 weeks.

Nature of the Toxic Reactions to Gold: In 43 (86 per cent) of the cases, the toxic reaction to gold consisted of pruritus, dermatitis or stomatitis. There were four cases of toxic bone marrow depression (thrombocytopenia, granulocytopenia and hypoplastic anemia), two cases of hepatitis and one of nephritis.

Interval between the Onset of the Toxic Gold Reaction and the Initiation of BAL Therapy: The interval between diagnosis of a toxic reaction to gold and initiation of BAL therapy ranged widely, from only 30 hours to more than one year. Results of BAL therapy generally varied inversely with the duration of this interval. The best results were obtained when treatment was started early, and in those individuals who did not receive BAL for weeks or months after the onset of symptoms results were as a rule inferior.

Method of Administration of BAL: Variations in the dosage schedules employed were notable and prevented a satisfactory analysis. In most of the cases, BAL was administered intramuscularly in the form of a 10 per cent solution in oil. The total dose ranged from a single injection of 100 mg. given in one day to 11,900 mg. given over a period of eight weeks. As a rule, doses of 2.5 to 3.0 mg. per kilogram of body weight every four hours were prescribed for cases of moderate severity. Once improvement was observed, the interval between doses was extended to eight, 12 or 24 hours, depending upon the judgment of the attending physician, and treatment was continued until the desired clinical improvement was obtained.

Results of BAL Therapy: In a majority of the cases, the response to BAL was described in terms varying from "good" to "immediate" or "dramatic." In some cases improvement occurred in 24 hours, while in others the response of the patient was more gradual. In patients with dermatitis accompanied by pruritus, improvement in pruritus occurred within a day or two, followed more slowly by resolution of objective skin lesions. Therapeutic results with BAL were considered satisfactory in 47 of the 50 cases

reviewed. Failure was reported in two cases of dermatitis and one of hypoplastic anemia.

Toxic Reactions to BAL: BAL possesses an inherent toxicity, and undesirable side reactions were not infrequent, though they were rarely of such nature as to necessitate cessation of therapy. Local abscess formation at the site of injection, sometimes requiring incision and drainage, was observed in a few instances. More frequently, local pain at the injection site was encountered. Flushing of the face, lacrimation, salivation, nausea, vomiting, substernal compression, transient hypertension or pain in the abdomen and extremities was often noted. These symptoms came on shortly after injection and rarely lasted more than an hour, so that they had largely disappeared by the time the succeeding dose was administered.

Discussion

On the basis of published reports 2,3-dimercaptopropanol has proved to be an effective antagonist to toxic effects of gold in over 90 per cent of cases in which it was employed. The average recommended dose of 2.5 to 3.0 mg. per kilogram of body weight appears to be effective in most cases when administered at intervals of four hours, or less frequently according to the dictates of individual cases. Doses up to 4 or 5 mg. per kilogram of body weight may be tolerated with minimal or no side effects.

The mechanism by which BAL acts as an antidote in heavy metal intoxications has been the subject of much investigation. It has been stated that heavy metals exert toxic effects by combining with sulfhydryl groups in protein fractions of essential cellular enzymes to form stable metal-protein combinations in tissues. This is believed to paralyze enzymatic action. BAL is thought to compete successfully for gold with its own sulfhydryl groups, thus relieving a biochemical block and permitting the cellular enzyme systems to return to normal function.[1] The resulting BAL-gold complex is inert. Increased urinary excretion of gold [2] has been described following the administration of BAL, but this is not an essential part of the process. It is perhaps appropriate at this point to note that there is no apparent correlation between amount of gold administered and development of toxic reactions. This has led to the suggestion that the so-called "toxic" reactions to gold may actually be a manifestation of hypersensitivity rather than a true toxic state.[5]

BAL is rapidly destroyed in the body; hence, duration of the therapeutic effect of any single dose is limited. By the same token, toxic effects are not cumulative if the interval between injections is at least three hours. It is probable that in man there is a considerable range between the therapeutic and the toxic dose. Lethal effects of excess 2,3-dimercaptopropanol, as observed in laboratory experiments with animals, are probably due to inactivation of enzyme systems containing an essential metallic component. Side reactions to BAL usually begin within 20 minutes of the injection and

subside in 45 to 120 minutes. These may take the form of local pain, salivation, metallic taste in the mouth, lacrimation, nausea, vomiting and flushing, or other evidences of autonomic stimulation. The use of orally administered ephedrine prior to each dose of BAL has been recommended to alleviate these uncomfortable reactions.[6] Although repeated intramuscular injections have not reportedly produced sensitization to BAL, local applications to the skin have done so.[4]

It has been emphasized repeatedly that success of BAL therapy depends in part upon early administration to prevent irreversible damage to essential enzyme systems and progression of symptoms. In nine of the case reports reviewed, BAL therapy was delayed for three months or more after onset of signs of gold toxicity, and was partially or totally ineffective in one-third of this group. In addition to prompt recognition of gold toxicity and initiation of therapy, adequate dosage is important. Among the cases surveyed, there were seven instances in which symptoms of gold toxicity recurred during or following a course of BAL therapy, and one case wherein a first course of treatment was only partially effective. In all eight, however, additional BAL resulted in complete clinical response. Improvement of joint symptoms has been described following appearance of gold toxicity, and, conversely, relapse of symptoms has been observed following successful therapy with BAL.

Case Reports

Case 1. A 48 year old unmarried white woman was admitted to the hospital November 7, 1948, complaining of pain and swelling of fingers, shoulders, elbows and knees for one year. Symptoms had become increasingly severe, and at the time of admission the patient was unable to dress herself, could not climb stairs and walked with considerable difficulty. The significant physical findings were limited to the musculoskeletal system. The neck was stiff and motion in any direction was painful. There was kyphosis of the dorsal spine. The shoulders and elbows were tender but not swollen, and permitted a full range of motion. The metacarpophalangeal joints and the proximal row of interphalangeal joints of the hands were swollen, exhibited a faint bluish discoloration and were moderately tender. Motion was restricted to the extent that the patient was unable to close her fists. The knees and ankles were tender but not swollen. The metatarsophalangeal joints were thickened and tender.

Laboratory Data: Hemoglobin, 16 gm.; red blood cells, 5.0 million per cu. mm.; color index, 1.0, hematocrit, 47; erythrocyte sedimentation rate (Wintrobe) 47 mm. in 1 hour (corrected); white blood count, 7,900 cells per cu. mm.; differential: segmented polys, 42; nonsegmented polys, 19; eosinophils, 2; basophils, 1; lymphocytes, 20; monocytes, 16. Serum urea nitrogen and glucose were within normal limits. The blood Kahn test was negative. Urinalysis revealed no abnormalities. An electrocardiogram and a chest roentgenogram were within normal limits. A film of the right knee revealed spur formation on the superior aspect of the patella and minimal spur formation on the tibial spines. There was osteoporosis of all of the bones of the right hand and wrist, with moderate narrowing of the joint spaces of the wrist.

Therapy consisted of symptomatic measures for relief of pain. In addition, the patient was treated with physical therapy, two 250 c.c. doses of 0.1 per cent pro-

caine intravenously, two sessions of two hours each in a fever cabinet, and a single intravenous dose of 15,000,000 typhoid organisms. The otolaryngologic consultant found infected tonsils. These were removed without incident under local anesthesia and the patient made an uneventful recovery. She was given 250 c.c. of whole blood following surgery and was discharged without having made any notable progress as regards the arthritis.

Following discharge, treatment with gold salts was begun. Two 10 mg. doses of gold sodium thiosulfate were administered intramuscularly one week apart. Approximately 72 hours following the second injection, the patient's temperature rose to 104° F., flushing of the face and chest appeared, and she felt extremely weak and experienced nausea and vomiting. These symptoms were accompanied by lessening of the arthritic complaints. One day after the appearance of these symptoms (December 18, 1948), the patient was re-admitted to the hospital. On physical examination, she appeared to be acutely ill. The rectal temperature was 103.2° F. A macular, morbiliform rash which blanched on pressure was noted on the face and on the upper part of the chest and back. The abdomen and upper portions of the arms were also involved. No petechiae were noted on the skin or mucous membranes. The physical examination was otherwise unchanged from the previous admission.

Laboratory Data: Red blood count, 3.46 million cells per cu. mm.; white blood count, 4,200; differential: segmented polys, 80; nonsegmented polys, 6; lymphocytes, 12; eosinophils, 2. Urinalysis: 2 plus albumin; 8 to 10 white blood cells and 0 to 2 red blood cells per high power field; rare finely granular casts.

The clinical diagnosis was acute gold intoxication. Treatment was started at once with injections of BAL (1.5 c.c. of a 10 per cent solution) every four hours. An infusion of 10 per cent glucose in saline and 500 c.c. of whole blood were administered. In addition, ascorbic acid and calcium gluconate by mouth, and crude liver extract and penicillin by intramuscular injection were prescribed.

During the first 30 hours after admission, the temperature rose as high as 105.2° F. Seven doses of BAL were given during this period. On the second hospital day the white blood count fell to 3,500 cells per cubic millimeter, and moderate albuminuria persisted. Clinically, the patient appeared improved. On the third hospital day the improvement continued. The rash receded slowly, but the fever ranged as high as 103.4° F. Five 1.5 c.c. doses of BAL were administered. Examination of the blood at this time revealed the following: hemoglobin, 11.1 gm.; red blood cells, 3.59 million per cubic millimeter; erythrocyte sedimentation rate, 48 (corrected 34 mm./hr.); platelets, 462,000. The white blood count was 5,250 cells, with a normal differential. On the fourth hospital day all medication was discontinued except for BAL, only three doses of which were administered. The rash was markedly diminished, although the patient continued to complain of fatigue. The temperature rose as high as 102.4° F. During the subsequent two days, BAL was administered twice daily in the same dosage. Clinical improvement was maintained and the maximum temperature was only 101.4° F. On the sixth hospital day BAL was discontinued, after a total of 28.5 c.c. (2,850 mg.) had been administered. The patient was discharged on the ninth hospital day afebrile and free of any signs of rash. Examination of the blood prior to discharge revealed a red count of 4.2 million cells per cubic millimeter; hemoglobin, 13.4 gm., and a white count of 6,100 cells per cubic millimeter. After discharge, the patient remained free of symptoms of gold toxicity until her death from unrelated causes about two years later.

Comment: This patient presented signs of a violent systemic reaction to gold accompanied by a diffuse skin rash. Improvement, which was evident within 24 hours of the institution of BAL therapy, continued slowly

but steadily thereafter. Although the patient received certain additional therapeutic measures during the first few days, our past experience suggests that the rapid recovery was not attributable in any significant degree to these measures, but was due solely to the action of BAL.

Case 2. A 16 year old white unmarried female was first seen in the out-patient department on January 18, 1946, having been referred from another institution with a diagnosis of "chronic ankylosing polyarthritis" of some 10 years' duration. Previous to being seen at the clinic, she had received physical therapy, foreign protein injections and treatment by cast immobilization.

In November, 1946, an arthroplasty was performed on the left elbow. In May, 1947, the patient was seen in the Arthritis Clinic and a diagnosis of juvenile rheumatoid arthritis (Still's disease) was made. Physical findings included flexion deformity of the right elbow and ankylosis of both wrists. All of the metacarpophalangeal joints of the left hand and the first, second and third joints on the right hand were swollen and tender. The right knee was swollen and tender and was distended by excessive amounts of fluid. Moderate quadriceps atrophy was present bilaterally. Only five to 10 degrees of motion were possible in the right ankle. The metatarsophalangeal joints were thickened and were the sites of flexion deformities.

On July 2, 1947, the patient was started on weekly intramuscular gold sodium thiosulfate, together with active and passive exercises. At that time the red blood cell count was 4.2 million, the platelet count 357,000 per cubic millimeter, and a urinalysis was negative. The initial dose was 5 mg., followed by two doses of 10 mg. and two doses of 15 mg. each. Thereafter, the dose was 25 mg. Subjective relief of the arthritic symptoms was noted. On October 20, 1947, urinalysis revealed a trace of albumin, 3 to 5 red blood cells per high power field and many epithelial cells. The red blood cell count was 4.8 million and the platelets were 229,000 per cubic millimeter. At this time the total amount of gold compound administered was 180 mg. Because of the urinary findings, therapy was discontinued. Repeated urinalyses were negative in November, and on December 8, 1947, gold therapy was resumed in doses of 25 mg. weekly. The urine was negative and the red blood cell and platelet counts remained normal until April 22, 1948. On that date the urine contained 2 plus albumin, one to two white blood cells per high power field, and many epithelial cells. The red blood cell count was 4.3 million, and the platelet count 134,000 per cubic millimeter. Gold therapy was discontinued, the patient having received a total of 605 mg. On April 26, urinalysis revealed 4 plus albumin, five to 10 white blood cells and occasional red blood cells per high power field. Because of the evidence of renal irritation, the patient was referred without delay to the hospital.

Physical examination on admission revealed a well developed, well nourished white female weighing 60 kg., who did not appear acutely ill. The rectal temperature was 100.6° F. and the pulse 108. The blood pressure was 125/80 mm. of Hg. Positive physical findings were limited to the joints as described above. The admission urinalysis revealed 4 plus albumin, three to five hyaline and granular casts, 15 to 20 red blood cells and 10 to 15 white blood cells per high power field. A diagnosis of gold nephritis was made and immediate therapy with BAL was instituted. The initial dose was 5 mg. per kilogram of body weight (300 mg.), followed by doses of 3 mg. per kilo (180 mg.) every four hours. On the following day, the temperature was normal and continued so throughout the hospital stay. The electrocardiogram and chest film were reported as within normal limits. X-rays of the affected joints revealed narrowing or obliteration of the joint spaces and cartilage destruction. The findings were interpreted as compatible with long-standing rheu-

matoid arthritis. The total blood count and the differential smear were normal, and the sedimentation rate (Wintrobe) was 10 mm. per hour. The serum urea nitrogen was 15 mg. per cent and the creatinine was 1.0 mg. per cent. The serum glucose, chlorides, carbon dioxide combining power, calcium, phosphorus, alkaline and acid phosphatases, cholesterol and esters, thymol turbidity and total proteins were all within normal limits. The cephalin cholesterol reaction was 2 plus. The blood Kahn test was negative. Urinalysis revealed the following: pH, 4.5; specific gravity, 1.030; albumin, 4 plus; acetone, 2 plus; occasional hyaline and finely granular casts; occasional shadow red blood cells and white cells. No gold was detected in the urine. On the third hospital day the patient continued to receive 180 mg. of BAL at four hour intervals. The blood pressure was 125/70 mm. of Hg, and the patient's only complaint was of pain at the site of the BAL injections. Urinalysis revealed a pH of 4.5; specific gravity, 1.027; albumin, 2 plus; two to three white blood cells, and occasional red blood cells per high power field. The Esbach determination for urinary protein was 0.06 per cent. On the fourth hospital day the blood pressure was 122/78 mm. of Hg. The BAL was reduced to 180 mg. four times daily. The urine was reported as showing 1 plus albumin, one to two white blood cells and occasional red blood cells per high power field. The Esbach determination was 0.02 per cent. The next day the BAL was further reduced to two doses daily and continued on that schedule for the next two days. Daily urinalyses continued to be negative for gold and showed continuing clearing of the sediment. On the seventh hospital day, only one dose of BAL was given. The patient was discharged on the eleventh hospital day with an essentially normal urine.

Comment: In this case, signs of renal irritation considered to be due to gold intoxication were detected early and responded promptly to the administration of BAL.

Summary and Conclusions

Fifty reported cases of gold intoxication occurring during the course of therapy of rheumatoid arthritis and treated with 2,3-dimercaptopropanol are reviewed and some of the salient features analyzed. Two additional cases are presented in detail. The greatest proportion of the untoward reactions to gold encountered clinically are manifested in the skin and mucous membranes, but parenchymatous organs may be affected as well. British anti-lewisite is an effective therapeutic agent in over 90 per cent of all cases of toxicity due to gold. The importance of early institution of adequate therapy is stressed. Unpleasant side reactions from BAL therapy are fairly common, but treatment rarely if ever must be withheld for this reason. The availability of a satisfactory agent with which to combat toxic reactions from gold represents a valuable addition to our therapeutic armamentarium. It is not a substitute for careful observation of the patient under chrysotherapy, but should offer some sense of security to the clinician who would otherwise fear to employ gold.

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THE SIGNIFICANCE OF MORTALITY STATISTICS IN MEDICAL RESEARCH: AN ANALYSIS OF 1,000 DEATHS AT THE PHILADELPHIA GENERAL HOSPITAL *

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Statistics collected in large hospitals are the basis for a great many studies, some of which are valuable from a medical standpoint, while others draw conclusions which have at best only a surface accuracy.

Often these reports are based upon analyses of autopsy data, because the information is more complete, detailed and consistent than may be obtained from case histories. If, for example, one examines autopsy reports of patients who have died from a particular disease and assembles some unique data with respect to these patients, one often asks, "How far can I generalize from the autopsy reports of one hospital?" The urge to move quickly from the specific to the general is strong and difficult to resist.

Not all patients who die in a hospital are autopsied. If the autopsied deaths differ from the nonautopsied deaths in certain characteristics (for example, age, sex, color, etc.), these differences must be known to make the findings applicable to total deaths from that disease in the hospital.

When the generalization can be applied to all deaths in the hospital, the investigator may then wish to apply his findings to a population outside of the hospital—for example, an entire city. It may then be necessary to determine what differences, if any, exist in the distribution between those deaths which occur in his institution, and those occurring in other hospitals, or outside of hospitals entirely.

Procedure

To determine what differences exist between autopsied deaths and total deaths in the Philadelphia General Hospital, and between total deaths in the hospital and deaths in the city of Philadelphia, an analysis was made of 1,000 consecutive deaths, both autopsied and not autopsied, which occurred in the Philadelphia General Hospital from April to July, 1949.

In this report we used only chief (or primary) diagnoses in those cases for which several causes of death were given. While we recognize the inherent errors of diagnosis and classification, we believe that the data presented here are nevertheless valid for the purposes for which they are used.

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From the Philadelphia General Hospital.

Results

Race: In this group 60 per cent of all deaths were among whites, 40 per cent among Negroes. It was found, however, that 61 per cent of the Negro deaths were autopsied, as compared with only 41 per cent of the white deaths. There were no significant differences between male and female rates in each group.

Table I

Mortality and Autopsy Statistics: Philadelphia General Hospital (April–July, 1949) and City of Philadelphia, 1948

	Philadelphia General Hospital			Distribution of Deaths in Per Cent		Average Age at Death* (years)	
	No. of Deaths*	No. of Autopsies	Autopsy Rates	Phila.	P.G.H.	Phila.	P.G.H.
White							
Male	360	153	43	45	36		
Female	237	89	38	38	24		
Total	597	242	41	83	60	62.9	65.8
Negro							
Male	175	105	60	9	21		
Female	166	104	63	8	19		
Total	341	209	61	17	40	49.9	51.0
Total							
Male	535	258	48	54	57	59.0	60.9
Female	403	193	48	46	43	62.1	59.8
Grand Total	938	451	48%	100%	100%	60.4	60.4

* Excludes 62 newborn deaths.

It can also be seen (table 1) that Negroes constitute a smaller segment of the deaths in the City of Philadelphia than in the hospital. Hence, in this hospital, not only are there relatively more Negro deaths than in the general population but more of them are autopsied. Therefore, autopsy statistics, uncorrected, may give a false picture of the racial incidence of diseases.

Age: The young were autopsied more than the old. Of deaths occurring in those 19 years or younger, 79 per cent were autopsied, as compared with 27 per cent of those in the age group 80 years or older.* (Table 2 shows these percentages by color.)

The age distributions in the statistics from the hospital and the city are remarkably similar, showing that data based on this factor are valid. The racial distribution, however, is not parallel, especially in the younger age group (table 2). This may be due to the shorter life expectancy of Negroes, so that they form an increasingly smaller portion of older age groups.

* It is interesting to note that this was not influenced by coroner's cases. During the period from which the 1,000 deaths were analyzed, there were 202 coroner's cases. The average age of the coroner's cases did not differ from the average age of the noncoroner's cases; and while 44 per cent of the 1,000 deaths were in persons less than 60 years of age, 43 per cent of the coroner's cases were in that age group.

TABLE II

Age Distribution by Race and Comparison of Hospital and City Figures

Age at Death	Autopsy Rate			Distribution of Deaths		Percentage Negro	
	White	Negro	Total	Phila.	P.G.H.	Phila.	P.G.H.
0–19*	50%	82%	79%	8%	8%	32%	91%
20–39	50	57	55	6	8	37	74
40–59	50	63	56	27	28	24	46
60–79	41	60	46	46	44	11	26
80 and over	22	53	27	13	12	6	15
				100%	100%		

* Excluding newborn.

Hospitalization: The autopsy rate decreased as the length of hospitalization increased. Excluding newborn, 79 per cent of deaths in those hospitalized for less than one day were autopsied, while only 25 per cent were autopsied following hospitalization for one year or more.

Type of Disease: Patients dying from less common diseases were autopsied somewhat more often than those dying from the leading causes of death. Among 788 deaths due to the 21 most common causes of death, 43 per cent were autopsied, while 57 per cent of the 212 deaths due to rarer causes were necropsied. Table 3 shows the autopsy rates of the 10 leading causes of death at the Philadelphia General Hospital. The majority (63 per cent) of deaths from tuberculosis were not autopsied.

Furthermore, it appears that while only 5 per cent of deaths diagnosed as cerebral embolism or thrombosis were autopsied, 71 per cent of those diagnosed as cerebral softening (encephalomalacia) were autopsied. The explanation of this unusual finding is a local matter of classification. Although many patients were diagnosed clinically as having died from cerebral embolism or thrombosis, the pathologic and final statement of the cause of death for this type of case was cerebral encephalomalacia, and the case was

TABLE III

Autopsy Rates for 565 Deaths Among 10 Most Common Individual Causes of Death: Philadelphia General Hospital (April–July, 1949)

Leading Causes of Death	Total No. of Deaths	Autopsy Rate Total	Autopsy Rate of White Deaths	Autopsy Rate of Negro Deaths
Tuberculosis of the respiratory system	120	37%	28%	44%
Hypertensive cardiovascular disease	65	48	37	55
Cerebral softening	65	71	59	86
Arteriosclerotic heart disease	58	53	48	75
Premature birth	57	14	0	15
Cancer of the digestive system	49	51	50	79
Cerebral embolism or thrombosis	41	5	3	10
Cerebral hemorrhage	40	53	38	79
Arteriosclerosis (except heart disease)	36	39	30	67
Bronchopneumonia	34	38	35	50

so listed in our files. Data for the City of Philadelphia show that there were less than half as many cases of encephalomalacia for the entire city in a year than there were in the Philadelphia General Hospital in four months. The explanation is that the office of Vital Statistics in the city accepts the diagnosis of cause of death which appears on the death certificate, and does not change it when a different pathologic diagnosis is made. Furthermore, in this hospital the neuropathologic diagnosis is based on the lesion and not on the etiology. Hence, the comparison of mortality statistics must take into consideration variations in the policies of different institutions.

TABLE IV

Distribution of Causes of Deaths by Location, Race and Sex

Causes of Death	Percentage Distribution		Percentage Negro		Percentage Female	
	Phila.	P.G.H.	Phila.	P.G.H.	Phila.	P.G.H.
Infectious and parasitic disease	5.4%	13.5%	42%	56%*	32%	33%
Cancers and other tumors	16.8	12.2	12	35*	50	34*
Rheumatic, nutritional, endocrine dis.	3.6	4.9	14	27*	68	65
Dis. of blood and blood-making organs	0.8	0.9	12	44*	44	22
Chronic poisonings and intoxications	0.2	0.8	26	38	21	13
Dis. of nervous system	8.0	19.1	17	35*	55	59
Dis. of circulatory system	39.3	20.0	13	35*	44	40
Dis. of respiratory system	4.1	5.4	21	26	42	33
Dis. of digestive system	4.1	4.5	13	38*	42	44
Dis. of genitourinary system	6.7	4.3	18	54*	49	26*
Dis. of pregnancy and childbirth	0.2	0.0	42	—†	100	—†
Dis. of skin and cellular tissues	0.1	0.6	21	17	63	50
Dis. of bones and locomotor organs	0.0	0.2	10	50	30	—†
Congenital malformations	1.3	0.5	17	40	44	20
Dis. of early infancy	3.4	6.2	35	92*	43	42
Senility	0.3	3.0	26	17	49	70*
Violent and accidental deaths	5.6	3.9	21	8	33	39
Ill-defined causes of death	0.1	0.0	27	—‡	24	—‡
Total	100.0	100.0	17%	40%*	46%	43%

* Statistically significant differences.
† No deaths.
‡ None in this category.

With this information, and the adjustment of the various ratios, one can arrive at a picture of both autopsied and nonautopsied deaths in the hospital. However, in Philadelphia only about one death in 10 occurs at the Philadelphia General Hospital. It will be shown that there are some differences between the deaths in the Philadelphia General Hospital and total deaths in the city. The differences may become important when applied to a particular research problem.

Table 4 shows the distribution of all deaths by major classification of causes for the city and for the hospital. Diseases of the circulatory system are statistically more important in the city than in the hospital, whereas diseases of the nervous system, and infectious and parasitic diseases (which

include tuberculosis) rank high in the hospital. This may be explained by the weighting of statistics in favor of neurologic and tuberculosis deaths at the hospital because of the large services for these patients. (These departments form 35.7 per cent of the hospital census.)

Table 4 also shows what percentage of deaths are Negro and what percentage female for the major causes of death. In most cases, but not all, the percentage of Negroes is higher at Philadelphia General Hospital than in the city, probably because of the higher Negro census at the hospital. (Significant differences by Fisher's "T" test between the city and the hospital are starred.) In short, mortality data based on a general hospital's experience may not be expected to resemble vital statistics accumulated from wider sources, i.e., a city.

Discussion

What is a legitimate use of autopsy data? To illustrate the problem of the validity of an autopsy aliquot, we will use data from a study of racial factors in the incidence of cirrhosis of the liver.[1]

Table V

Racial Distribution of Deaths in Cirrhosis of the Liver Compared to the Clinical Diagnosis and to General Autopsy Rates

	Fatal Cirrhosis[1]			Total Hospital This Study		Department Medicine 1950	
	Total No. Cases	No. Autopsied	% Autopsied	% Autopsied	Total Deaths	% Autopsied	Total Deaths
Negro	36	26	72.2	61	341	62.9	394
White	281	140	49.9	41	597	46.2	606
Total	317	166	52.5	48	938	52.8	1,000

Table 5 summarizes the findings. Using only autopsy figures, it will be seen that at the Philadelphia General Hospital, at least, the ratio of white to Negro among 166 autopsied cirrhotics was 5.4:1. Assuming, however (for the argument), that the clinical diagnosis was correct in every instance, it can be seen that the white to Negro ratio among all fatal cirrhotics seen between April, 1942, and December, 1950, was 8.8:1. More important, about three fourths of cirrhotic Negroes were autopsied, but only one-half of the whites. Therefore, autopsy statistics were weighted towards the Negro because of a higher autopsy rate, within one disease group, than among whites.

Furthermore, the average hospital autopsy rates would be of no avail (table 5), since the autopsy percentage in this disease did not resemble the total hospital figures, nor would it be expected to.

To complicate matters further, it was found in a survey of deaths on the general medical service of the hospital in 1950 (1,000 deaths) that,

while 43.8 per cent of the average daily census on Medicine was Negro, 39.4 per cent of the deaths were among Negroes but 47 per cent of the autopsied subjects were Negro. In other words, the total autopsy population (from Medicine) may have resembled the Medical Ward census, but there was a significant difference in the racial incidence in one specific disease entity as observed post mortem.

Only a most cursory examination of deaths by diseases has been attempted here. The object has been to give some idea of the scope of the problem which exists when medical findings from small groups of cases are expected to be applied to broad populations. In an individual case, thought must be given to the characteristics of the sample studied as compared to the area of application.

Summary

An analysis of 1,000 consecutive deaths at the Philadelphia General Hospital reveals the many variable factors which modify conclusions drawn from autopsy statistics.

It was noted that more Negro dead were autopsied than white dead. The younger the patient, the shorter his stay in the hospital; the less common his disease, the higher the probabilities that he will be autopsied if he dies.

The incidence of certain diagnosis (such as cerebral thrombosis or embolism) depends upon the autopsy, which verifies or disproves the diagnosis.

Differences were noted and discussed between hospital data and vital statistics from the City of Philadelphia.

All of these factors must be considered in any interpretation of data gleaned from the hospital records.

Acknowledgment

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THE DEVELOPMENT OF GASTRIC CARCINOMA IN PERNICIOUS ANEMIA *

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IN 1876 Quincke [1] first reported the occurrence of a carcinoma of the stomach in a patient suffering from pernicious anemia. It was not until the third decade of this century, however, that investigators began statistical studies of the incidence of gastric malignancy and premalignant lesions in large series of pernicious anemia cases. More recently, Rigler, Kaplan and Fink [2] found that as high as 8 per cent of their pernicious anemia patients developed gastric carcinoma, and an additional 7 per cent had gastric polyps, making a total incidence of 15 per cent of their series with malignant or premalignant gastric lesions. Our interest in this subject was aroused by these reports of high incidence, and this study was therefore undertaken.

The principal series reported in the literature are listed in table 1. They comprise both living and autopsy groups. The incidence of gastric carcinoma in the combined living series is 1.7 per cent and in the autopsy groups 8.3 per cent.

METHOD OF STUDY

An attempt was made to reach all patients who had come to the clinic for the diagnosis or treatment of pernicious anemia. The criteria for the diagnosis of pernicious anemia were critically analyzed in each case, and careful follow-up observations were made whenever possible. The diagnosis was confirmed in cases in which macrocytic hyperchromic anemia accompanied by an achlorhydria responded to liver therapy. Gastric roentgenographic studies were done when the patient could come to the clinic, and in most cases bone marrow studies were carried out.

RESULTS

Of a total of 341 cases of pernicious anemia, 233 had one or more roentgenographic examinations of the stomach. The total series of cases was followed for from one month to 24 years after the development of symptoms due to pernicious anemia, with an average follow-up of five and nine-tenths years for those patients who had roentgenograms and of six and eight-tenths years for the total group. Four cases of carcinoma of the stomach appeared in this group, an incidence of gastric carcinoma of 1.1 per cent of the total group and 1.7 per cent of the group with roentgenograms. In addition to these four patients, there were two patients with

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TABLE I

The Incidence of Malignant and Premalignant Gastric Lesions in Pernicious Anemia as Compiled from the Literature

Year	Author	Number of Cases	Carcinoma		Polyps	
			Number	Per Cent	Number	Per Cent
1923	Giffin and Bowler[6]	628	1	0.16	—	—
1931	Strandell[7]	117	4	3.4	—	—
1933	Wilkinson[8]	370	2	0.27	—	—
1933	Conner and Birkeland[9]	658	4	0.6	—	—
1934	Brown[10] (autopsy)	151	1	0.66	12	8.0
1936	Murphy and Howard[11]	440	4	0.99	1	0.22
1938	Washburn and Rozendaal[12]	906	16	1.76	8	0.88
1939	Jenner[13]	181	8	4.4	3	1.6
1942	Doehring and Eusterman[14]	1,014	17	1.7	4	0.39
1943	Jankelson et al.[15]	100	4	4.0	—	—
1944	Myers[16]	85	3	4.0	—	—
1944	Frank[17]	188	5	2.65	—	—
1945	Kaplan and Rigler[3] (autopsy)	293	36	12.3	—	—
1947	Rigler and Kaplan*[18]	259	18	6.9	17	6.6
1948	Wallace[19]	203	2	1.4	—	—
1950	State et al.[4]	94	3	3.2	4.0	4.2

Note: Unless otherwise noted, each series represents the study of living patients.
* This series includes a smaller series reported by Rigler, Kaplan and Fink[3] in 1945.

pernicious anemia who were sent to the clinic because of gastric carcinoma, and one patient whose megaloblastic anemia did not develop until several years after gastrectomy for carcinoma of the stomach. These studies represent a total of 2,321 years of observation in these 341 pernicious anemia cases, or a total of 1,383 years of roentgenographic observation in the 233 patients so examined. It seems obvious to us that the two pernicious anemia patients sent to the clinic for operation on their gastric lesions should not be included in the series purporting to represent the incidence of gastric carcinoma in the general pernicious anemia population.

CASE REPORTS

Case 1. This 61 year old man entered the clinic in January, 1944. Thirteen years previously he had had a subtotal gastrectomy for a peptic ulcer. Following this, he had been well until eight months before entry, since which time he had noted weakness and epigastric discomfort and had lost 10 pounds in weight.

On physical examination he was pale, but there were no other significant findings. Laboratory studies showed a hemoglobin of 9.7 gm. per cent, a red blood cell count of 3,280,000, and a white blood cell count of 4,400. The blood smear showed hypochromia, anisocytosis and poikilocytosis. The gastric analysis showed no free hydrochloric acid after histamine. The gastrointestinal series, barium enema and roentgenograms of the chest were normal. He responded well to iron therapy, and his red blood count and hemoglobin rose to normal levels. When seen 12 months later, however, he again complained of fatigue and weakness, and studies showed a macrocytic hyperchromic anemia with a hemoglobin of 9.1 gm. per cent, a red blood cell count of 2,500,000, and a hematocrit of 27 per cent. The bone marrow puncture smear taken from the sternal area showed megaloblastic hyperplasia. There was neurologic evidence of combined system disease at that time also. On liver

therapy the blood rapidly returned to normal over the course of a five week period and the patient became asymptomatic. He remained well on liver treatment for about two years, when he began having frequent episodes of epigastric distress and vomiting. Roentgenograms of the stomach revealed a rigid area proximal to the gastroenterostomy stoma, with mucosal changes suggesting a neoplasm. Operation was advised but refused; not until eight months later would he permit operation, and at that time an adenocarcinoma was found. He died one month later.

Comment: The occurrence of a hypochromic anemia 13 years after a subtotal gastrectomy which responded to iron therapy but which was followed one year later by a hyperchromic macrocytic megaloblastic type of anemia suggests that these hematologic abnormalities may have been secondary to the gastrectomy rather than to pernicious anemia in the true sense of the term. However this may have been, the patient did develop carcinoma of the stomach after the liver deficiency anemia appeared, and he must therefore be included in the group under discussion.

Case 2. This 58 year old woman was admitted to the clinic in October, 1946, complaining of weakness and difficulty in walking. A diagnosis of pernicious anemia had been made 14 months previously by a well known hematologist, and the patient had been treated with liver until two months prior to her admission. The roentgenograms of the stomach were normal. Neurologically, she showed evidence of combined system disease, and although the blood picture at that time was normal, intensive liver therapy was instituted. The patient improved markedly and was eventually able to walk normally. She then continued well for 18 months, at which time her ataxia returned in spite of continued liver therapy. Six months later, when she again returned to the clinic, the blood studies showed a mild hypochromia. Three stools were positive for blood, but roentgenograms of the stomach were refused until four months later, which was two and one-half years after her original admission, at which time she was hospitalized because of chronic nephritis and uremia. A roentgenogram of the stomach at this time revealed polyposis with one suggestively malignant polyp. She died three months later but no autopsy was permitted.

Comment: Although the diagnosis of gastric polyposis and malignancy could not be finally proved, we believe that this case represents an example of malignant degeneration of the gastric mucosa in a patient with pernicious anemia.

Case 3. This 58 year old woman entered the clinic in October, 1946, complaining of progressive weakness. One year previously her local physician had given her some liver injections for anemia, with alleviation of her symptoms, but these had recurred when she stopped her treatment. Also, the patient had recently developed abdominal distention and paresthesias of the feet. She was pale and the vibratory sense was absent in the ankles. The hemoglobin was 7.3 gm. per cent, the red blood cell count 2,300,000, the white blood cell count 2,900, and the hematocrit 23 per cent. The smear showed some macrocytosis, and the gastric analysis revealed no free acid. The patient responded rapidly to liver therapy and within two months her blood picture was normal. She returned two years later with a six months' complaint of anorexia and vomiting, and an upper abdominal mass could be palpated which on roentgenograms appeared to be a malignant lesion of the stomach. At operation an inoperable carcinoma of the stomach was found.

Comment: This represents a clear-cut case of gastric carcinoma in a patient with pernicious anemia.

Case 4. This 61 year old man entered the clinic in March, 1942, because of exertional dyspnea. The patient appeared chronically ill. He was pale and his tongue was atrophic. The vibratory sense was impaired. The hemoglobin was 10.0 gm. per cent, the red blood cell count 2,220,000, the hematocrit 35 per cent and the white blood cell count 3,850. The smear showed macrocytosis and poikilocytosis, and many multilobulated polymorphonuclear leukocytes. The gastric analysis showed no free hydrochloric acid after histamine. A roentgenogram of the stomach was normal. The patient was treated with liver and within one month his blood count had returned to normal. He continued on this therapy at home and was well for four and one-half years, when he again became anemic in spite of adequate liver therapy. Laboratory examination at this time showed a hypochromic anemia, and roentgenograms of the stomach demonstrated a sizable filling defect in the antrum. At operation a carcinoma was found, and the patient died eight months later.

Comment: This is a clear cut case of the development of gastric cancer in a patient with pernicious anemia.

Discussion

An attempt to establish the true incidence of malignant and premalignant gastric lesions in patients having pernicious anemia is of fundamental importance, for when this is known, it can then be decided whether every patient with pernicious anemia should have frequent gastric roentgenographic examinations. Some of the reports of the past decade suggest a high incidence of malignant and premalignant lesions—as high as 15 per cent in living patients in one study.[2] When the larger series of living patients are totaled, we find an incidence of 1.7 per cent of gastric carcinoma and 1.3 per cent of gastric polyps. The former figure is the same as ours.

The accuracy of the diagnosis of pernicious anemia is of the greatest importance in a study of this kind. We have insisted on including only those cases which showed a macrocytic anemia occurring in an achlorhydric patient and which have responded to liver therapy. Bone marrow studies were done in most instances but not all. In each case a megaloblastic bone marrow was found. In one case only (described in detail under report of case 2), the diagnosis was made elsewhere in a well known hematology clinic; the patient had responded to liver therapy and came to us with combined system disease following a lapse of treatment.

Great care must be exercised in the compilation and study of statistics. It is our opinion that part of the difference in the reported incidence noted above is the result of different methods of study. An important source of error may arise from the fact that cases of gastric carcinoma tend to gravitate to the large medical centers, thus giving these centers an abnormally high incidence of both gastric carcinoma in general and gastric carcinoma occurring in pernicious anemia. The difficulty in distinguishing the megaloblastic macrocytic anemia developing in patients with carcinoma of the stomach from true pernicious anemia is well recognized and raises another problem in establishing the true incidence. We believe that the attempt of Kaplan and Rigler [2] to interpolate and arrive at a probable incidence of gastric carcinoma in patients with pernicious anemia may have led to a falsely high incidence in their autopsy series.

State et al.[4] have studied a series of 1,137 symptomless patients with achlorhydria and found an incidence of 0.53 per cent of gastric carcinoma and, also, an incidence of 2.6 per cent of gastric polyps on a single roentgenographic examination. St. John [5] and associates examined 2,413 patients over 50 years of age without gastric complaints and on a single examination found two gastric carcinomas, one lymphosarcoma and no polyps. The incidence of gastric carcinoma, therefore, was 0.08 per cent in the latter series. If further investigation confirms this incidence of gastric carcinoma in the older population, with and without achlorhydria, this will give us an incidence in our series of patients with roentgenograms about three times as great as in symptomless achlorhydric patients. It must be remembered, however, that these series are not truly comparable, because our series of patients was followed over many years and many were examined on several occasions, while in both the other series the patients were examined but once.

As mentioned before, two patients sent to the clinic with carcinoma of the stomach were known to have had pernicious anemia previously. These were excluded from the statistical portion of the study because they would weight the incidence of gastric carcinoma abnormally.

While we do not attempt to decide at what incidence of gastric carcinoma routine annual or semi-annual roentgenologic examinations become practical, we think it is obvious that all people over the age of 45 cannot be subjected to such a study. Likewise, it is obvious that if the true incidence of malignant and premalignant lesions in any group of patients even approached 15 per cent, then such routine roentgenograms would be mandatory. Whether the incidence of 1.7 per cent over a period of several years' observation is sufficiently high to warrant such periodic roentgenologic examinations is problematic. We believe, however, that the average incidence of all major series in the literature of 1.7 per cent and our own incidence in patients examined by roentgen-ray of 1.7 per cent make the necessity of routine roentgenologic examinations much less certain. It is interesting to note that, out of all of the large number of routine roentgenologic examinations done in our 233 cases, no gastric lesions were found in symptomless patients. Specific symptoms led to the roentgenologic diagnosis of gastric carcinoma in all four of the malignant cases. That roentgenologic study should be carried out in pernicious anemia patients with gastric symptoms or when a hypochromic anemia develops needs no comment.

If yearly routine roentgenologic examinations had been done in our series of patients who had roentgenograms, 346 negative roentgenologic studies would have been carried out for each patient found with gastric carcinoma.

Summary

The incidence of malignant and premalignant gastric lesions in patients with pernicious anemia has been reported to be as high as 15 per cent.

Our series of pernicious anemia cases was studied from this point of view and an incidence of 1.7 per cent of malignant gastric lesions was found in the patients examined roentgenographically.

The incidence in our series agrees closely with the combined average incidence in the major series reported in the literature.

The advisability of frequent gastric roentgenologic examination of pernicious anemia patients is discussed.

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LIPID STUDIES IN PATIENTS WITH ADVANCED DIABETIC ATHEROSCLEROSIS *

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In recent years, interest in the problem of human atherosclerosis has been great. Since the early observations on atheromatous lesions in cholesterol-fed rabbits,[1, 2] there have been many studies on the possible rôle of elevated blood cholesterol in the genesis of atherosclerosis. The work of Gofman and his co-workers [3] has been of interest in this connection through their demonstration of a technic for measuring cholesterol-bearing lipoproteins in serum. The group of molecules known as the Sf_{10-20} group, according to Svedberg's designation of flotation densities, has been reported to be elevated in individuals with coronary artery disease and is thought by the above investigators to be directly concerned in the atherosclerotic process. Elevation of other serum lipid fractions in atherosclerotic patients has been a controversial subject, as has also the effect of "lipotropic substances" on these lipids.[4-10]

The present study was designed to determine the levels of a number of lipid entities in the blood of a group of patients with advanced atherosclerosis in association with diabetes, and to determine the effects of certain pharmacologic agents upon these lipids.

Procedure

The patients selected consisted of 24 elderly hospitalized diabetics (seven men and 17 women with diabetes of varying duration), several of whom had had leg amputations for diabetic gangrene, myocardial infarctions and cerebral accidents (table 1).

Patients were maintained on relatively constant "diabetic diets." After two control specimens on consecutive days, bloods were drawn in the fasting state at weekly intervals while the patients were on one of three medication programs. The serum was analyzed for free and total cholesterol, for lipid-phosphorus and for lipoprotein (Sf_{10-20}). Insulin requirement and average semiquantitative urinary glucose excretion were recorded. Medications

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From the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, California.

With the technical assistance of Nancy Dawson and Sadie Smyrl.

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TABLE I

Patient	Sex	Age	Insulin	Initial Cholesterol	Initial Lipoprotein	Dorsalis Pedis Pulsation	Amputation	Current Gangrene	Known Myocardial Infarction	CVA
P. A.	M	62	No	211.5 ±0.24%	72.0 ±9.72%	0	1 accidental	0	0	0
E. C.	F	86	Yes	222.5 ±1.12%	77.5 ±13.55%	0	2	0	0	0
L. F.	F	62	Yes	144.5 ±0.35%	55.0 ±14.55%	2	0	0	0	0
M. G.	F	82	Yes	208.5 ±0.72%	60.0 ±13.33%	0	0	0	0	Yes
C. L.	F	73	Yes	272.5 ±2.75%	176 (one only)	0	0	0	0	Yes
G. M.	F	82	Yes	267.0 ±5.99%	95.0 ±5.26%	0	0	0	0	0
R. P.	F	70	Yes	134.0 ±2.99%	33.5 ±1.49%	0	0	0	Yes	0
T. V.	M	71	Yes	207.0 ±3.86%	97.0 ±11.34%	0	1 osteo	0	0	0
J. B.	M	71	No	202.0 ±0.99%	29.0 ±0%	2	0	0	0	Yes
J. Co.	F	81	Yes	226.5 ±1.55%	43.0 ±20.93%	0	0	0	0	0
P. F.	F	75	Yes	183.0 ±2.73%	57.0 ±17.54%	2	0	0	0	Yes
A. F.	M	72	Yes	259.5 ±0.58%	92.5 ±4.86%	1	0	0	0	0
J. L.	F	60	Yes	232.5 ±5.38%	66.0 ±1.52%	0	1	0	0	0
T. N.	F	81	No	214.5 ±3.03%	42.5 ±24.71%	2	0	0	0	0
M. S.	M	69	Yes	172.5 ±0.29%	29.0 ±10.34%	0	1 later	Yes	0	0
E. S.	F	72	No	218.5 ±1.60%	33.5 ±31.34%	0	2	0	0	0
J. Ca.	M	69	Yes	176 (one only)	43 (one only)	0	2	0	0	0
M. D.	F	68	Yes	271.5 ±2.03%	142.5 ±15.79%	1	0	0	0	0
A. G.	F	71	Yes	268.0 ±1.12%	125.0 ±2.40%	0	0	Yes	0	0
J. M.	F	61	Yes	224.0 ±2.68%	81.0 ±3.70%	2	0	0	0	Yes
A. M.	F	60	Yes	220.5 ±4.31%	84.5 ±1.78%	2	0	0	0	Yes
P. M.	M	84	Yes	193.0 ±1.04%	44.0 ±18.18%	0	2	0	0	0
V. P.	F	80	Yes	190.0 ±4.74%	45.5 ±16.48%	2	0	0	0	Yes
M. P.	F	88	No	198.5 ±1.76%	60.0 ±1.67%	0	0	0	0	0

administered were choline, inositol and testosterone propionate, respectively, because of their known or supposed effects on serum lipids and/or on the atherosclerotic process.

Eight patients received 6 gm. of choline citrate daily for 31 days. Eight patients received 9 gm. of inositol daily for 27 days, and eight patients received 25 mg. of testosterone propionate daily intramuscularly, for varying periods.

METHODS

Cholesterol was determined by the method of Michaels et al.,[11] in which the cholesterol digitonide is determined turbidimetrically. The normal range is essentially the same by this method as that reported by Schoenheimer and Sperry.[12] Lipid phosphorus was determined by the method of Youngburg and Youngburg.[13] Lipoprotein Sf_{10-20} was determined by an ultracentrifugation technic.*

RESULTS

A study of the effects of the three medications on these blood constituents failed to reveal consistent alterations which could be ascribed to the medications in the case of choline and inositol. In the case of testosterone, three patients appeared to have a decrease in the levels of cholesterol and lipoprotein during therapy (figure 1). Consistent changes in the diabetic state were not observed during or following the periods of treatment. A decrease in insulin requirement, however, was noted in four patients on testosterone.

* Grateful acknowledgment is made to Dr. John Gofman for performance of these determinations.

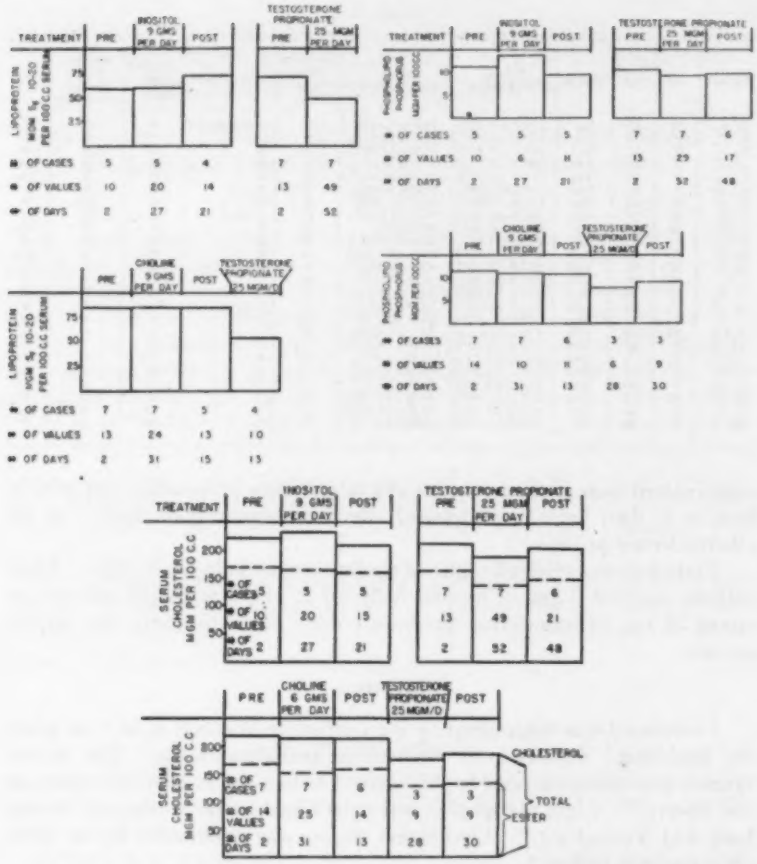


FIG. 1. Examination of the data suggests that inositol and choline had no effect on any of the lipid entities, but that testosterone propionate may have decreased the serum concentration of all of the lipid fractions studied. Further work will be required before one will know whether these observations are statistically significant.

Taking the group as a whole, a considerable spread in the values of the various lipid components was observed (table 2). This spread was particularly great in the case of the lipoproteins, with a coefficient of variation equal to 48 per cent, compared to coefficients of 20 per cent for total cholesterol, 21 per cent for cholesterol esters and 22 per cent for lipid phosphorus. The difference between two daily control values in individual patients was ± 10.93 per cent in the case of lipoprotein and ± 2.25 per cent in the case of total cholesterol. The mean cholesterol level was 203.1 mg. per cent in

the seven males and 217.4 mg. per cent in the 17 females. In a control group of hospitalized elderly patients, none of whom had had myocardial infarctions, strokes, amputations or diabetes, the mean level of cholesterol was found to be 169.5 mg. per cent in 10 males and 158 mg. per cent in 13 females.

TABLE II

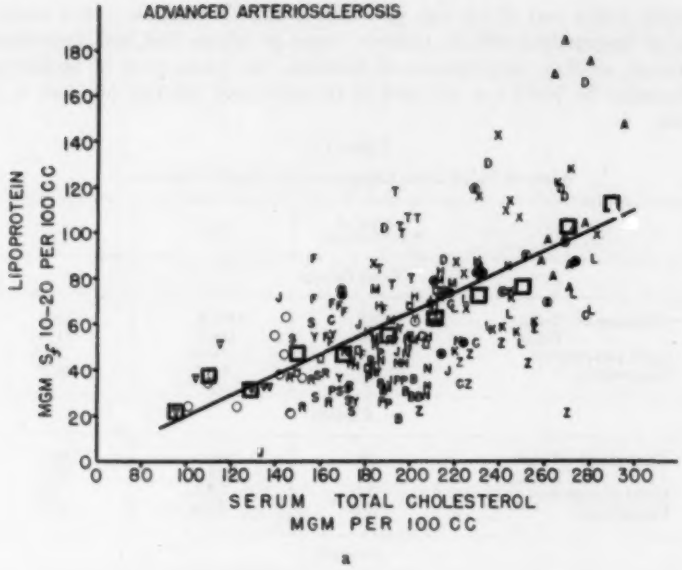
Values of Blood Lipid Components in Elderly Diabetics

	Number of Determinations	Mean	S. D.
Total Group			
Cholesterol—Total	208	202.8	41.1
Esters	206	148.6	31.0
Lipid phosphorus	166	10.09	2.18
Lipoprotein	208	63.0	30.5
Choline			
Cholesterol—Total	39	206.1	45.2
Esters	39	149.3	33.8
Lipid phosphorus	34	10.56	2.24
Lipoprotein	39	86.8	37.4
Inositol			
Cholesterol—Total	70	212.0	40.1
Esters	69	156.1	31.0
Lipid phosphorus	47	10.66	2.37
Lipoprotein	70	56.0	24.4
Testosterone Propionate			
Cholesterol—Total	71	199.5	32.2
Esters	70	146.0	24.8
Lipid phosphorus	61	9.72	1.73
Lipoprotein	71	58.7	27.4

An analysis of our data reveals a significant correlation between the levels of many of the lipid components studied (figure 2). The correlation coefficient between total cholesterol and lipoprotein is 0.613; between esterified cholesterol and lipoprotein, 0.530; between lipid phosphorus and lipoprotein, 0.453, and between esterified cholesterol and lipid phosphorus, 0.671.

COMMENT

Under the conditions of this study, it appears that large doses of inositol and choline produced little or no alteration in the diabetic state or the levels of blood lipid components in these patients. The interpretation of the fall in lipid levels during and for a short period after testosterone therapy in some patients is not apparent at the present time. Further studies are in progress.


ADVANCED ARTERIOSCLEROSIS
LIPOPROTEIN
MGM Sf 10-20 PER 100 CC
0
20
40
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160
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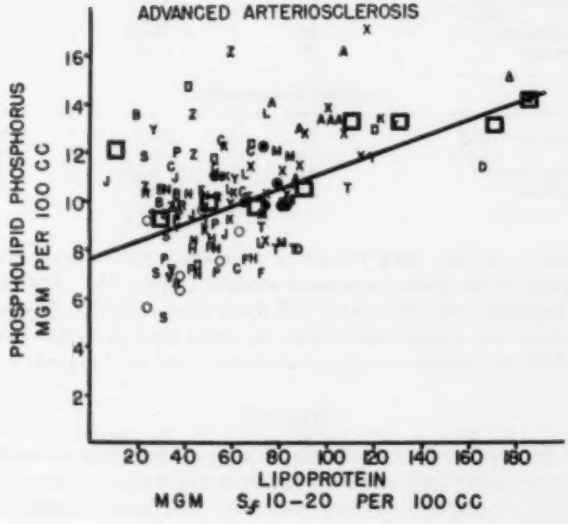
0 80 100 120 140 160 180 200 220 240 260 280 300
SERUM TOTAL CHOLESTEROL
MGM PER 100 CC

a


ADVANCED ARTERIOSCLEROSIS
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LIPOPROTEIN
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b

FIG. 2.

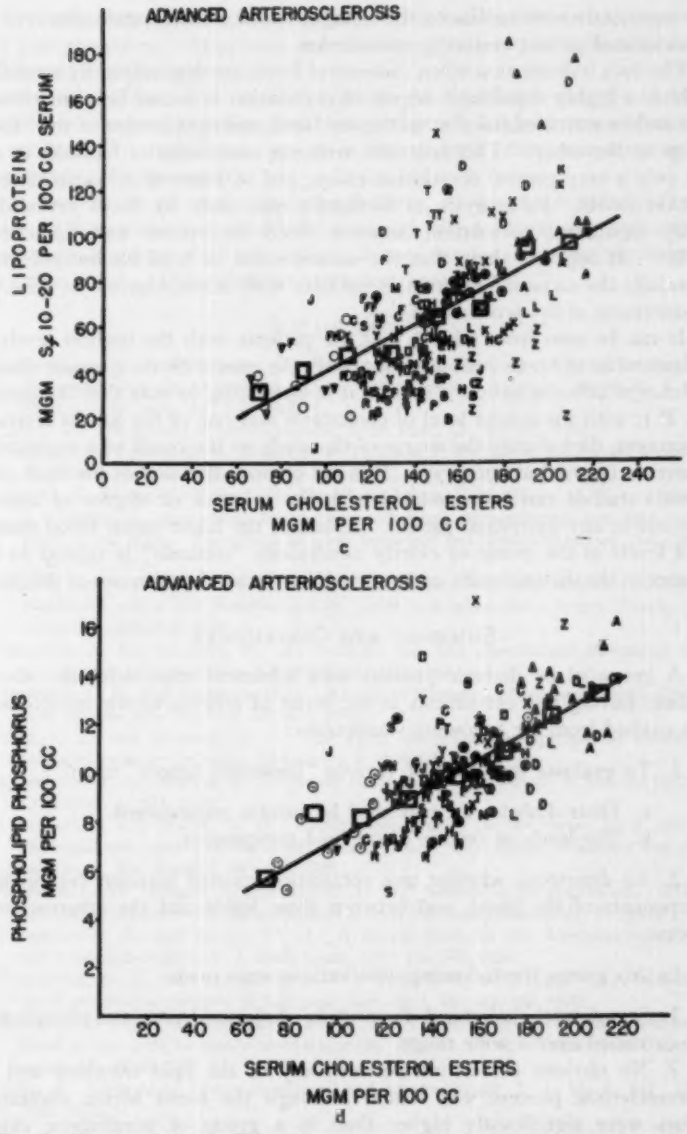

FIG. 2. The correlation coefficient between total cholesterol and lipoprotein is 0.613; between esterified cholesterol and lipoprotein, 0.531; between lipid phosphorus and lipoprotein, 0.453, and between esterified cholesterol and lipid phosphorus, 0.671. The first and last figures have high statistical significance in terms of "linear correlation" of the respective entities.

The same statement applies to the changes in the diabetic state observed in an occasional patient receiving testosterone.

The data indicate that when cholesterol levels are determined by a reliable method, a highly significant degree of correlation is found between cholesterol and its esterified fraction on the one hand, and lipoproteins of the Sf_{10-20} group on the other. This contrasts with the conclusion of Gofman et al.[3] that only a very general correlation exists, and of Jones et al.[14] that no correlation exists. Re-analysis of Gofman's own data by Keys revealed a highly significant correlation between blood cholesterol and lipoprotein levels.[15] It appears, then, that the measurement of total cholesterol gives essentially the same information in patients with atherosclerosis as does the measurement of lipoproteins, Sf_{10-20}.

It can be seen from table 1 that the patients with the highest levels of cholesterol or of lipoprotein are not always the ones with the greatest clinical evidence of atherosclerosis. Indeed, it is interesting to note that the patient (R. P.), with the lowest level of cholesterol and one of the lowest levels of lipoprotein, died during the course of the study as the result of a myocardial infarction (proved at autopsy). It is not obvious that any of the lipid components studied can be correlated with the presence or degree of atherosclerosis in any individual patient. Whether the lower mean blood cholesterol levels in the group of elderly nondiabetic "controls" is related to the absence of the diabetic state, or to some other factor, is unknown at this time.

Summary and Conclusions

A group of 24 diabetic patients with advanced atherosclerosis, several of them having lost extremities as the result of atherosclerotic involvement, was studied from the following standpoints:

1. To evaluate the effect of various "lipotropic agents" upon:
   a. Their diabetes as evidenced by insulin requirement.
   b. The levels of certain blood lipid components.

2. To determine whether any correlation existed between certain lipid components of the blood, and between these lipids and the atherosclerotic process.

In this group, the following observations were made:

1. Serum total cholesterol, lipoprotein, cholesterol ester and phospholipid values varied over a wide range.

2. No obvious correlation between any of the lipid fractions and the atherosclerotic process was found, although the mean serum cholesterol values were significantly higher than in a group of nondiabetic elderly "controls."

3. Linear mathematical correlation was noted between the lipoprotein and total cholesterol, lipoprotein and cholesterol esters, and cholesterol esters and serum phospholipids.

4. Under the conditions of this study, no significant changes in blood lipids were observed in patients receiving relatively large amounts of inositol or choline. No significant change in the diabetic state was observed in response to the same agents.

5. Depression of serum cholesterol esters, of serum phospholipids and of serum lipoprotein was observed in several patients receiving testosterone propionate in a dose of 25 mg. daily. Some changes in insulin requirement were also noted. These changes were not constant.

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THE USE OF ACTH AND CORTISONE IN IDIOPATHIC THROMBOCYTOPENIC PURPURA AND IDIOPATHIC ACQUIRED HEMOLYTIC ANEMIA *

By Muriel C. Meyers, *Ann Arbor,* Stanley Miller, *Baltimore, Maryland,* James W. Linman, and Frank H. Bethell, F.A.C.P., *Ann Arbor, Michigan*

ACTH and cortisone have been put to trial in the treatment of a variety of hematologic disorders, to emerge as agents of therapeutic importance in thrombocytopenic purpura and acquired hemolytic anemia. In discussing these conditions it is implied that reference is made to the so-called idiopathic forms of the disease.

Thrombocytopenic purpura assumes a variety of clinical forms, varying widely in severity but having in common hemorrhagic manifestations associated with thrombocytopenia, increased capillary fragility, prolonged bleeding time and defective clot retraction. The marrow is active and essentially normal. The clinical course may be acute and fulminating, active but stationary, or cyclic in nature. Permanent remissions may occur spontaneously. Removal of the spleen may result in either lasting or temporary remission, or it may fail to alter the course of the disease. The disorder is of unknown cause but is believed to result from reticuloendothelial dysfunction, especially within the spleen. The spleen has been incriminated alternatively as the site of excessive sequestration and increased destruction of platelets,[1] and as the source of a humoral agent which inhibits maturation and release of platelets from the marrow [2] or increases their destruction in the circulating blood.[3, 4]

Acquired hemolytic anemia is similarly of unknown cause, variable in the severity and acuteness of its clinical manifestations, and subject to spontaneous remissions. Criteria for diagnosis include reticulocytosis, increased bile pigment metabolism, and evidences of autoimmunization. Although less frequently than in thrombocytopenic purpura, splenectomy may be curative. The recent demonstration of a thrombocyte agglutinating factor in the serum of patients with thrombocytopenic purpura suggests a common etiology for the two disorders which may be observed to occur simultaneously.[4]

Since the spleen is a lymphoreticular organ, knowledge that the administration of ACTH or cortisone modifies lymphoid and reticuloendothelial activity [5-8] provided a rational basis for the use of these agents in the management of patients with thrombocytopenic purpura and acquired hemolytic anemia.

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Over the past 22 months we have treated 17 consecutive patients with thrombocytopenic purpura and seven patients with acquired hemolytic anemia with either ACTH or cortisone or both. The patients with purpura consisted of five males and 12 females, ranging in age from nine years to 72 years. The hemolytic anemia group was comprised of two men and five women, aged 16 to 72 years.

Platelets were enumerated by the indirect method, employing brilliant cresyl blue films counterstained with Wright's stain. By this method, normal values range from 200,000 to 400,000 per cubic millimeter. Direct and indirect Coombs' tests, tests of serum with trypsinated cells and with normal compatible cells in human plasma and bovine albumin were used to detect autoimmunization. Studies of the marrow were performed on all patients.

Thrombocytopenic Purpura

In 12 of the 17 patients with thrombocytopenic purpura the response to the administration of ACTH or cortisone was excellent (table 1). The platelet counts and bleeding times returned to normal. Clinical symptoms

Table I

Thrombocytopenic Purpura Treated with ACTH and Cortisone

Degree and Duration of Response	
Complete sustained remission (16–22 months)	5
Complete followed by relapse and splenectomy	6
Complete followed by partial relapse	1*
Incomplete followed by relapse and splenectomy	4
Poor followed by relapse and splenectomy	1
Total number of patients	17
Number requiring splenectomy	11

* Splenectomy performed 5 months before treatment.

disappeared. In five of the 12 patients the remissions have been sustained for periods varying from 16 to 22 months. Seven of the 12 patients relapsed after the cessation of hormone therapy. One of these had previously failed to respond to splenectomy. In each of the other six a second or third remission was induced successfully, and while the hemorrhagic diathesis was under control splenectomy was performed without incident. Four patients had incomplete remissions. In each splenectomy was performed while still under hormone treatment. There have been no postoperative relapses. A single patient who had had a poor response to both ACTH and cortisone has had an excellent result from splenectomy.

Case Reports

Case 1. A 14 year old school girl had had purpura and menorrhagia for two months. The spleen was palpable. The platelet count was 4,700. The bleeding time was 15 minutes, and clot retraction was poor in 24 hours. No platelet budding from

marrow megakaryocytes was seen. ACTH, 100 mg. daily, was given for six days. Eosinopenia developed within 24 hours, a significant increase in platelets occurred within 36 hours, and normal platelet values were attained within five days. Concomitantly the bleeding time and clot retraction returned to normal. The spleen was no longer palpable, and the patient became asymptomatic. Upon withdrawal of the ACTH there was a slight transient decrease in platelets, followed by a rise to normal levels. Improvement has been maintained for 21 months (figure 1).

Case 2. A 43 year old male, two weeks prior to his initial visit, had had a sore throat followed by extensive purpura which persisted until admission. The platelet count was zero, the bleeding time was greater than 20 minutes, and no clot retraction was apparent after 24 hours. The marrow megakaryocytes were inactive. During the course of an eight day period when he received ACTH, 100 mg. daily, the 17-ketosteroid excretion and total white blood cell count rose but the eosinophils and

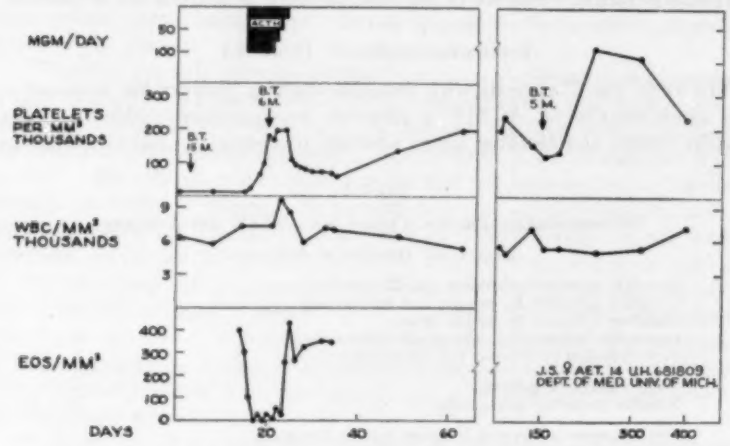
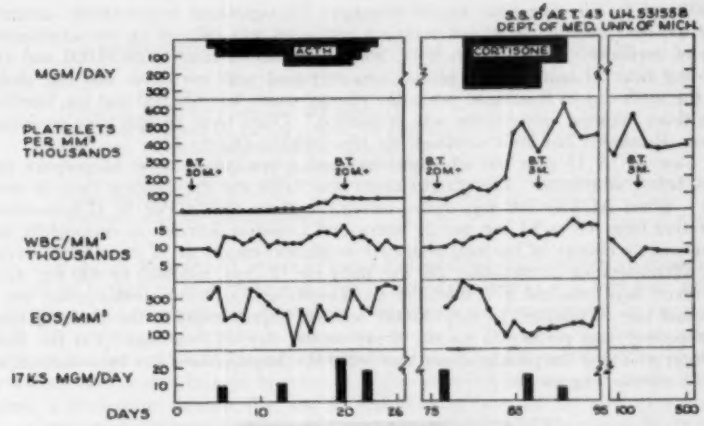


FIG. 1.

platelets were not affected appreciably. An increase in dosage of ACTH to 160 mg. daily for seven days was followed by marked clinical improvement, a further rise in 17-ketosteroid excretion, inconstant eosinopenia and a moderate rise in platelets to 85,000.

Two months later, although there had been no recurrence of purpura, the patient was re-admitted for cortisone therapy because of continued suboptimal thrombocyte counts and prolonged bleeding time. The initial platelet count was 106,400. After six days of cortisone, 300 mg. daily, the count was 453,600. Treatment was continued for a total of 14 days. Two days later the platelet count was 583,200. Improvement in bleeding time and clot retraction paralleled the rise in platelet count. Following cessation of treatment there was a slight transient decrease in platelets, but subsequently improvement has been maintained for 17 months (figure 2).

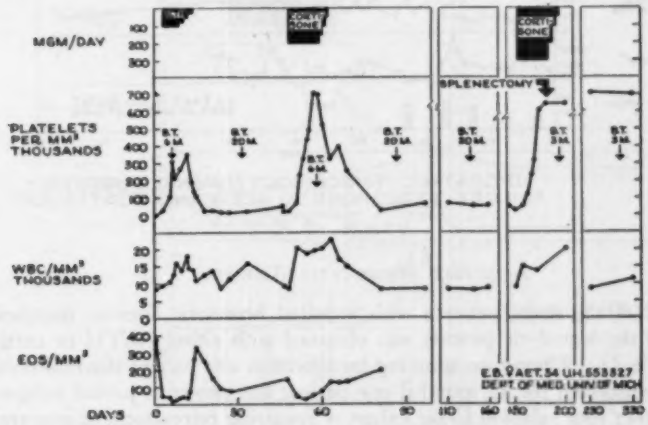
Case 3. A 34 year old woman had had her first episode of purpura at the age of 25. This was followed by a spontaneous remission, during which she had an un-



IDIOPATHIC THROMBOCYTOPENIC PURPURA
TREATED WITH ACTH & CORTISONE

FIG. 2.

eventful full term delivery. Six months before admission, purpura recurred and remained stationary. The clinical manifestations were minimal, but the platelet count was 9,000 and the bleeding time was 16 minutes. After three days of ACTH, 100 mg. daily, the platelet count was 336,000 and the bleeding time was six minutes. Treatment was discontinued after eight days. Four days later the platelet count was



IDIOPATHIC THROMBOCYTOPENIC PURPURA
TREATED WITH ACTH, CORTISONE & SPLENECTOMY

FIG. 3.

16,000 and the bleeding time was 20 minutes. No significant improvement occurred over the next month. A second transient remission was induced by the administration of cortisone. Five months later, when the platelet count was 50,000 and the bleeding time 20 minutes, the patient was retreated with cortisone, 300 mg. daily. On the tenth day of treatment, when the platelet count was 655,000 and the bleeding time three minutes, splenectomy was performed. There were no operative complications. Remission has been sustained for nine months (figure 3).

Case 4. A 15 year old schoolgirl had had a precipitous onset of purpura one week before admission. The platelet count was 4,000 and the bleeding time 19 minutes. When ACTH, 100 mg. daily, was given there was a rise in 17-ketosteroid excretion from 4.8 to 9.1 mg. per 24 hours, and a modest decrease in eosinophils, but there was no change in the total leukocyte or platelet counts or in the clinical status. The administration of cortisone, 200 mg. daily for 11 days, followed by 400 mg. daily for seven days, resulted in a transient eosinopenia and a definite leukocytosis, but a maximal rise in platelets to only 30,000, without improvement in the bleeding time. Splenectomy was performed on the thirty-second day of treatment. On the third postoperative day the platelet count was 665,000. Improvement has been maintained for 15 months (figure 4).

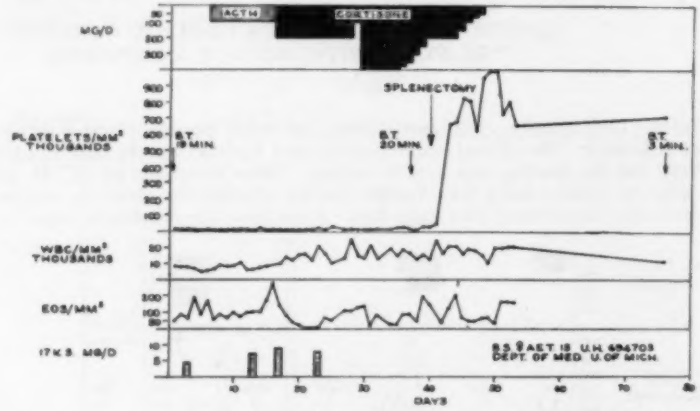


FIG. 4.

ACQUIRED HEMOLYTIC ANEMIA

In six of the seven patients with acquired hemolytic anemia, complete control of the hemolytic process was obtained with either ACTH or cortisone (table 2). Upon discontinuing treatment in one patient the remission has been sustained for 15 months, one patient has shown a partial relapse, and the other four relapsed to the extent of requiring retreatment in preparation for splenectomy. A single patient, in whom cortisone therapy appeared life-saving yet incapable of producing a complete remission, failed to attain normal values after splenectomy until cortisone treatment was re-instituted.

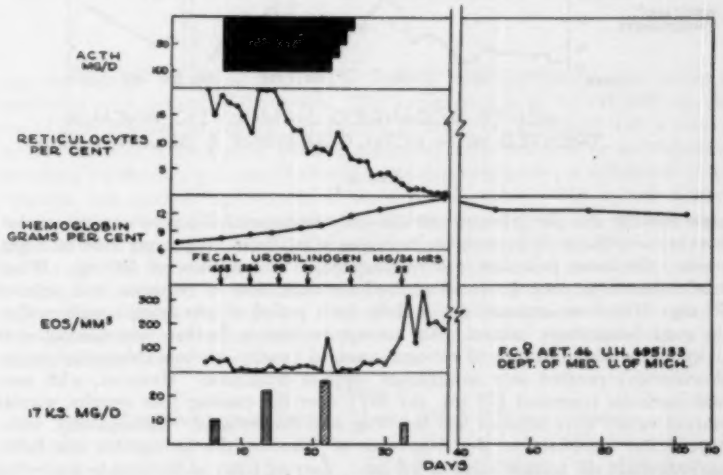
TABLE II

Acquired Hemolytic Anemia Treated with ACTH and Cortisone

Degree and Duration of Response	
Complete sustained remission (15 months)	1
Complete followed by partial relapse (6 months)	1
Complete followed by relapse and splenectomy	4
Incomplete followed by relapse and splenectomy	1
Total number of cases	7
Number requiring splenectomy	5

Case 5. A 46 year old practical nurse had suffered from recurrent episodes of anemia refractory to hematinics and requiring transfusions over a two year period. The spleen was enlarged, and incomplete antibodies were demonstrable in the serum. Red cell resistance to hypotonic saline was normal. The marrow showed marked erythrocytic hyperplasia. The administration of ACTH, 100 mg. daily for 21 days, was associated with a prompt increase in 17-ketosteroid excretion, a variable eosinopenia, a gradual progressive decrease in reticulocytes from 20 per cent to less than 1 per cent, a rise in hemoglobin from 7 gm. to 14.5 gm., and a decrease in 24 hour fecal urobilinogen excretion from 455 mg. to less than 100 mg. The spleen was no longer palpable. Although clinical and hematologic remission has been maintained for 15 months, incomplete antibodies in low titer have persisted intermittently in the serum (figure 5).

Case 6. A 65 year old woman had been remarkably well until three months before admission, when she developed weakness and jaundice. Six transfusions had resulted in no improvement. On admission she was acutely ill and moderately icteric,



ACUTE ACQUIRED HEMOLYTIC ANEMIA TREATED WITH ACTH

FIG. 5.

and the spleen was palpable 15 cm. below the costal margin. The marrow showed relative erythrogenic hyperplasia, and there was an increase in erythrocyte osmotic fragility. Incomplete antibodies were present in the serum. After six days of ACTH, 100 mg. daily, there was no clinical or hematologic improvement. Repeated transfusion of resuspended red cells, although not associated with reactions, did not increase the erythroid values. She was critically ill, with a hemoglobin of less than 3 gm. per cent, when cortisone therapy was instituted cautiously at a dose of 200 mg. per day. Although the hemoglobin did not rise, the cortisone was well tolerated and after five days was increased to 300 mg. per day. With continued transfusions the hemoglobin then rose to 8 gm. per cent. Clinical improvement was marked, but because of troublesome fluid retention the cortisone was reduced to 150 mg. per day and transfusions were discontinued. Her hematologic status remained stationary. On the thirty-first day, cortisone therapy was stopped and splenectomy performed.

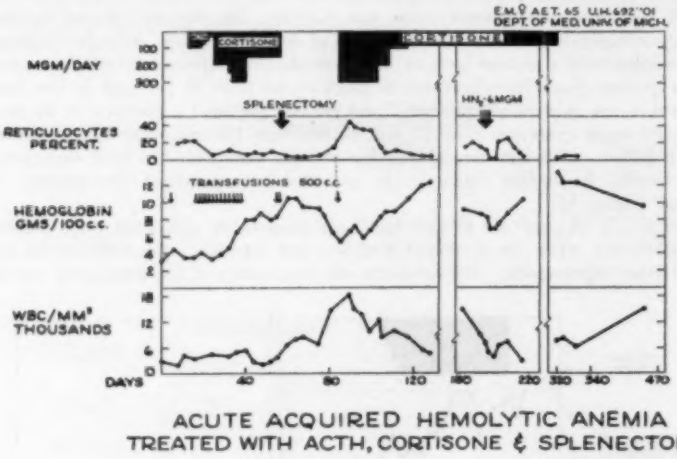
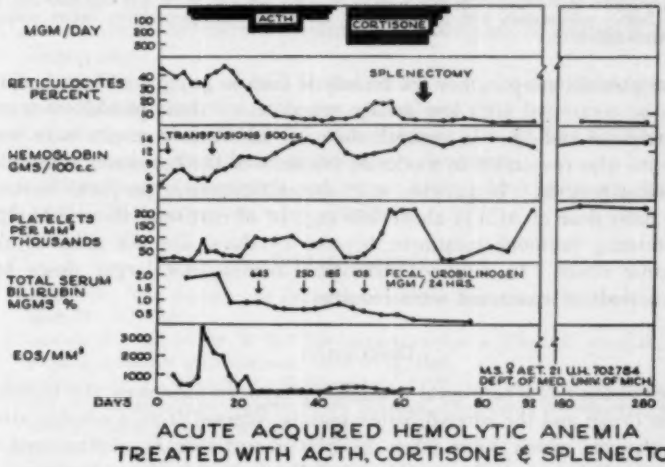


FIG. 6.

Wound healing was per primum, and the early postoperative course was uneventful. However, over the next 21 days the hemoglobin fell from 10 gm. per cent to 5 gm. per cent. Cortisone treatment was re-instituted, at a daily dose of 300 mg. When partial hematologic control was re-attained the daily dose of cortisone was reduced to 75 mg. This was continued uneventfully for a period of four months, with moderately good hematologic control. An attempt to modify further reticuloendothelial activity by the administration of nitrogen mustard (methyl-bis beta chloroethyl amine hydrochloride) resulted only in apparent myeloid depression. However, with continued cortisone treatment (75 mg. per day) over the ensuing four months, normal erythroid values were attained and the drug was discontinued. Subsequently, without particular symptoms or the recurrence of jaundice, the hemoglobin has fallen progressively to the present value of 9.5 gm. Varying titers of incomplete antibodies have persisted throughout her course* (figure 6).

*Over a period of 11 months this patient received 850 mg. of ACTH and 29.725 gm. of cortisone without demonstrable effect on the blood pressure or glucose tolerance.

Case 7. A 21 year old female, six weeks before admission, became ill with fever and malaise, followed in three weeks by frank jaundice with marked weakness. Numerous transfusions had been without effect. On admission she was acutely ill and mildly icteric, the spleen was enlarged, and there were scattered petechiae and ecchymoses. The hemoglobin was 4 gm. per cent, the reticulocytes were 45 per cent,



ACUTE ACQUIRED HEMOLYTIC ANEMIA
TREATED WITH ACTH, CORTISONE & SPLENECTOMY

FIG. 7.

and the platelet count was 5,000. The marrow was hyperplastic, and incomplete antibodies were present in the serum. The administration of ACTH, 100 mg. daily for 14 days followed by 160 mg. per day for 21 days, was associated with a transient marked increase in the already elevated eosinophil count, followed by an eosinopenia, decreased pigmentary evidence of excessive red cell destruction, a suboptimal platelet response, and marked improvement in the erythroid values. She became asymptomatic. When the ACTH was discontinued, however, clinical and hematologic relapse occurred promptly. The administration of cortisone, 300 mg. daily, was begun. By the eleventh day of treatment normal erythroid and platelet values were attained. On the nineteenth day of cortisone treatment, splenectomy was performed. Anemia did not recur postoperatively, but there was a severe transient thrombocytopenia. The patient has been under observation for nine months postoperatively without further relapse (figure 7).

TABLE III

Thrombocytopenic Purpura Treated with ACTH and Cortisone

Response	ACTH Mg./Day	Cortisone Mg./Day	Treatment Time Days	Days Required for Maximal Response
Good	100	200–300	8–15	3–11
Fair to poor	100–160	300–400	11–23	6–16

TABLE IV

Acquired Hemolytic Anemia Treated with ACTH and Cortisone

	ACTH	Cortisone
Dose/day, mg.	100–160	300
Treatment time, days	11–36	19–28
Days required to attain normal hemoglobin	6–26	12–24

Not included in these data is case 6, who received 850 mg. of ACTH and 6.25 gm. of cortisone before splenectomy and 23.575 gm. of cortisone after splenectomy before normal values were attained.

In neither the purpura nor the hemolytic anemia group could therapeutic failures be correlated with low dosage schedules or short periods of treatment (tables 3 and 4). In general, the most satisfactory results were seen in patients who responded to moderate amounts of the hormones after relatively short periods. In patients with thrombocytopenic purpura, increasing the daily dose of ACTH above 100 mg., or of cortisone above 300 mg., or continuing hormone treatment beyond 14 days, did not enhance the therapeutic effect. In acquired hemolytic anemia, not larger doses but longer periods of treatment were required.

DISCUSSION

The existence of a reciprocal relationship between the spleen as a lymphoreticular organ and the adrenal cortex may be inferred from a consideration of the changes which occur when ACTH or cortisone is administered to patients with hypersplenic conditions.[9, 10, 11] It is not clear, however, to what extent the changes that occur are attributable to myeloid stimulation as opposed to lymphoreticular inhibition. The absence of platelet budding from marrow megakaryocytes in patients with thrombocytopenia suggests myeloid stimulation as an important factor in the restoration of normal platelet values. However, decrease in an abnormal ability of the plasma to produce thrombocytopenia coincident with the administration of cortisone has been reported.[3] In acquired hemolytic anemia, myeloid stimulation appears to be unimportant, as erythrogenic hyperplasia of the marrow and increased reticulocyte counts in the peripheral blood are associated with activity of the disorder. When ACTH or cortisone is administered to patients with acquired hemolytic anemia, the changes that occur in antibody titer do not vary directly with changes in hemolytic activity. In general, the titers fall as hemolysis decreases.[9] However, in one patient (case 6), we observed a marked rise in the titer of autoimmune bodies at a time when clinical and hematologic remission was evident. It seems probable, therefore, that the administration of ACTH and cortisone in hypersplenic disorders may restore hematopoietic equilibrium through a combination of effects, including modification of immune body reactions, diminished splenic hypersequestration and hyperphagocytosis, and myeloid stimulation.

Conclusions

1. The administration of ACTH or cortisone may modify the course of thrombocytopenic purpura or acquired hemolytic anemia, producing changes that appear to be entirely analogous to those observed in spontaneous remissions.

2. When the remissions are not sustained, they are reproducible. ACTH and cortisone, therefore, afford valuable means of preparing patients for splenectomy.

3. Intensive courses of ACTH and cortisone in the immediate preoperative period do not interfere with wound healing.

4. Failure to respond to the administration of ACTH and cortisone does not preclude a therapeutic response to splenectomy.

5. Patients with incomplete remissions after splenectomy may be benefited by ACTH or cortisone administration.

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ANTIMICROBIAL THERAPY OF TUBERCULOSIS IN 1952 *

By H. Corwin Hinshaw, M.D., F.A.C.P., *San Francisco, California*

It has become almost traditional to open a discussion of this topic with the statement that antimicrobial drugs have yielded disappointing results in treatment of tuberculosis, having failed to provide the long sought cure. Actually, physicians familiar with tuberculosis therapy have never anticipated that any antimicrobial drug would cure this disease. Instead of being disappointed, such physicians have been constantly revising their opinions toward greater optimism, especially within the past two years. They have found increasing utility for these drugs, particularly in the treatment of the more chronic and destructive types of tuberculosis, as progress has been made in deferring the appearance of bacterial resistance to drugs, in avoiding signs of drug toxicity among patients treated, and in utilizing more definitive surgical procedures.

Some accepted principles of antimicrobial therapy in tuberculosis have been developed which can now be stated with considerable confidence.

1. Most patients with active tuberculous infection should receive antimicrobial drugs at some stage of treatment. Some physicians have advocated that *all* persons with active disease should be so treated.[1]

2. Such treatment should be prolonged and continuous, and maintained for a considerable time after all evidence of activity of the disease has ceased.[2]

3. Streptomycin and para-aminosalicylate should be used concurrently, rather than in sequence, in order to defer the appearance of bacteria resistant to the drugs, as was shown first in 1949.[3]

4. Streptomycin need not be administered every day, for similar results may be obtained when it is given every third day.[4]

5. Surgical extirpation of some destructive tuberculous lesions may well be deferred until many months of medical therapy have resolved all reversible disease.[2]

6. Principles established for pulmonary tuberculosis appear to apply to some types of extrapulmonary tuberculosis as well.

7. Principles established for streptomycin and para-aminosalicylate are likely to apply to other bacteriostatic drugs.

If it be true literally that all patients with active tuberculosis should receive continuous antimicrobial drug therapy until such time as the disease becomes inactive, the selection of candidates for treatment would be simplified. Some physicians have been unwilling to admit the universal applicabil-

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ity of this form of treatment, knowing well that many tuberculous infections are readily controlled by bed-rest, collapse therapy and surgery. Before all physicians can accept the principle of universal antimicrobial drug therapy, it must be demonstrated that the addition of such therapy either shortens the treatment appreciably or gives great promise of accomplishing a more lasting arrest of the disease, with a reduced hazard of late exacerbations during subsequent years.

There is a real danger that the universal use of antimicrobial drugs against active tuberculosis might foster neglect of other therapeutic efforts. Surely superior therapeutic results have been observed when judicious collapse therapy, prolonged bed-rest and surgical excision of any incurable localized destructive lesions have been combined with drug therapy. Indeed, the advent of potent antimicrobial drugs has made the management of tuberculosis more difficult and more exacting than it previously was. Instead of reducing the need for sanatorium beds and for the services of skilled physicians, modern treatment has increased the needs for such care, even while the death rate from tuberculosis has been declining sharply.

D'Esopo and his associates [2] have reported exceptionally fine therapeutic results from treating patients with pulmonary tuberculosis with antimicrobial drugs continuously for a year or longer without interruption. Relapse of disease due to drug-resistant tubercle bacilli very rarely occurs during a prolonged initial course of combined streptomycin and para-aminosalicylate therapy. Some interesting and even remarkable observations have been made by D'Esopo and his associates [2] when necrotic tuberculous pulmonary foci were examined following their surgical removal after many months of antimicrobial drug therapy. Such lesions often showed little or no histologic evidence of active disease, and the tubercle bacilli which were visible would not infect guinea pigs or grow in culture media. Whether these bacilli were dead or so disturbed in their metabolism as to be incapable of reproduction outside the human body has not been determined. It is possible that very prolonged therapy with streptomycin and para-aminosalicylate may produce a bactericidal effect in vivo!

The observation of Tempel and his associates [4] that streptomycin need be administered only every third day when combined with para-aminosalicylate therapy has been widely confirmed, and the extremely low toxicity of such a therapeutic regimen has done much to widen the applicability of antimicrobial therapy of tuberculosis. Such issues as the relative toxicity of streptomycin and dihydrostreptomycin lose significance when recognizable toxicity of either drug is so exceedingly rare if given under these conditions.

A crucial study is under way [5] to determine if highly purified streptomycin and dihydrostreptomycin have different neurotoxic potentialities and to determine, if possible, whether either drug has superior therapeutic pro-

perties. This project involves the utilization of these two drugs without knowledge by the physician as to which is being administered and should supply truly objective data when the study has been completed. Previous, less well controlled observations, probably employing drugs of varying purity, have produced varying opinions as to the neurotoxicity of dihydrostreptomycin.[6, 7]

There has been some shifting of opinion as to when necessary surgical resection of tuberculous pulmonary tissue should be carried out in relation to drug therapy. Formerly, it appeared logical to resect destructive lesions early in the course of medical treatment to avoid any possible tuberculous complication due to drug-resistant organisms. Recently the trend has been to await resolution of the reversible component of the infection, permitting more localized resection and at a time when the disease process has become inactive. When the latter course is followed tuberculous complications following surgery are very low, and frequently the surgeon finds it feasible to remove the residual lesion locally by "wedge resection" rather than by segmental or lobar resection.

The management of extrapulmonary tuberculosis frequently becomes the task of internist or specialty surgeon rather than of the physician specializing in thoracic disease. Antimicrobial drug therapy is directed against the same parasitic bacillus in all the tuberculous diseases, and it appears probable that the principles discussed above will apply not only to pulmonary tuberculosis and its complications but also to tuberculosis involving the peritoneum, the pericardium, the genitourinary tract, the gastrointestinal tract, the skeletal system and the lymphatic system. For each of these conditions, emphasis should be placed upon very long term therapy, perhaps one or two years, with potent antituberculosis drugs, and upon surgical treatment of destructive lesions when feasible.

Miliary tuberculosis and tuberculous meningitis constitute the most dangerous types of tuberculous disease, and despite the advances described in our knowledge of antimicrobial drugs the mortality rate remains high. Under such conditions it appears wise to recommend much higher doses of both streptomycin and para-aminosalicylate than for noncritical tuberculous infections. The parenteral administration of sodium para-aminosalicylate in massive doses (30 to 40 gm. per day), in addition to full doses of streptomycin daily, appears to offer a substantial hope of material reduction in mortality from these diseases.[8]

The fact that isonicotinic acid hydrazide appears in the cerebrospinal fluid in amounts theoretically adequate to control tuberculous infection[9] offers real hope that this newer drug may prove to be of additional value in treating tuberculous meningitis.

Isonicotinic acid hydrazide, recently recognized during investigation of the thiosemicarbazones, is a drug of great current interest and of real thera-

peutic promise.[10] Although no one has utilized this drug on sufficiently large numbers of patients for sufficiently long periods of time to know how it may compare with established antituberculosis drugs, evidence has developed that it may suppress tuberculous infection at least to a limited degree for at least a limited period of time in some but not in all clinical situations. Our experience with it on more than 100 patients [11] indicates that it is not a curative drug, for it does not rapidly eradicate tuberculous infection, but it acts as a symptomatic remedy and as a bacterial suppressive agent, in much the same manner qualitatively as do streptomycin and para-aminosalicylate. Whether it may be inferior or superior to established remedies remains to be determined. In either event, it appears to be one additional effective drug, to be used alone or, more probably, in combination with such a drug as streptomycin, and its appearance should be hailed as a substantial advance. Pyrazinamide is a related drug, with similar or more limited clinical potentialities, which is in need of more study.

Many patients and many physicians have registered disappointment following a trial of antimicrobial drug therapy in tuberculosis. These disappointments are usually attributable to brief or discontinuous courses of treatment, to inadequate bed-rest and lack of effective collapse therapy, or to failure to accept surgical treatment of destructive lesions, and to our tardy recognition of the necessity of combining two or more drugs.

The addition of new series of chemical compounds adds complexity to the problem, while increasing the effectiveness of those measures which can be used against this disease which is today the most significant bacterial infection of the human race.

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CASE REPORTS

LENGTH OF LIFE OF AN ADULT AFTER DEVELOPMENT OF COMPLETELY OBLITERATIVE CHRONIC CHOLANGITIS *

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No reference has been found as to possible length of life in an adult after complete irremediable obstruction of the common bile duct has occurred. Infants with congenital atresia of the bile ducts may live as long as 24 to 30 months, and Holt and McIntosh [1] mention one who lived for more than three years. The following case is presented to record the length of life of a 62 year old woman after the occurrence of completely obliterative chronic cholangitis involving all of the extrahepatic biliary radicals.

Case Report

A 62 year old white female housewife was first seen by a surgeon on February 16, 1948, because of intermittent right upper quadrant pain radiating to the right scapular region of two years' duration. The pains, which were precipitated by fatty foods, had gradually increased in severity, and the patient had lost 20 pounds in the preceding four months. There was no history of jaundice. The systems review and past medical and family histories were not significant. Physical examination was essentially negative except for slight right upper quadrant tenderness. The liver, gall-bladder and spleen were not palpable. Examination of the blood and urine was negative. Graham-Cole test revealed eight fairly large non-opaque stones within the gall-bladder.

On February 17 an "easy" cholecystectomy was done under spinal anesthesia. Pathologic diagnosis on the surgical specimen was chronic cholecystitis and cholelithiasis. Two days after operation slight clinical icterus was noted, and a copious bile drainage appeared from the abdominal wound. On the thirteenth postoperative day the icterus index was 20 units. On the twenty-seventh postoperative day the patient was discharged from the hospital with the abdominal wound well healed. There was no official note that the patient was jaundiced at the time of discharge, though the patient herself stated she was not.

On April 25, 1948 (the sixty-sixth postoperative day), the patient was re-admitted to the hospital because of marked jaundice and pruritus which had developed progressively since her discharge. Icterus index was 124 units; van den Bergh, positive, direct, 140 mg./100 c.c.; stool, negative for bile; bleeding time, 1.75 minutes; coagulation time, 6 minutes; erythrocyte count, 3.32 millions; hemoglobin, 90 per cent; leukocyte count, 5,000, with 70 per cent polymorphonuclear leukocytes; urine, slight trace of albumin, with a 2 plus bile reaction and a few coarsely granular casts.

Five days after admission an exploratory laparotomy was done under spinal anesthesia. Numerous adhesions were encountered. At the point where the cystic duct had been ligated an obstruction of the common bile duct due to scar tissue

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formation was found. The liver appeared normal, as it had at the first operation. However, aspiration of the hepatic duct yielded no bile. A portion of rubber catheter was inserted into the hepatic duct to the liver and extended through the common bile duct into the duodenum, the bile duct being closed completely over the catheter, and one "0" plain catgut suture being used to anchor the catheter to the duct wall. The pruritus lessened markedly and the patient's appetite remained good, but acholic stools and marked jaundice persisted. On May 10, 10 days after the biliary catheterization, the van den Bergh was positive, direct, 125 mg./100 c.c. Flat plate of the abdomen, three weeks after the exploration, revealed the catheter to be slipping down into the duodenum. The patient was referred to us on May 22, three months after her original cholecystectomy.

At that time the patient stated that color had returned to her stools and that she felt quite well, even though she was still markedly jaundiced. Since no bile had been found in the hepatic duct at the second operation, it was felt that the biliary obstruction might be on an intrahepatic basis and that further surgery was not indicated at that time. The patient was placed on a medical hepatic regimen, but seven days later the jaundice had deepened, and pruritus and acholic stools had returned. By June 4, 1948, the original incision had broken down and drained purulent material with no bile. The drainage ceased gradually, and on June 22 reëxploration was carried out. A complete fibrotic obliteration of all the extrahepatic bile ducts was observed. The hepatic ducts were traced up as far as possible into the hilum of the liver, but no bile-containing channel was found. The catheter which had been inserted into the bile ducts 53 days previously was not present. An anomalous relationship was noted in that the hepatic artery entered the liver just anterior to the exit of the bile ducts. No type of biliary anastomosis was possible under the presenting conditions. A section of the common bile duct taken at operation revealed a chronic fibrotic inflammatory process with complete obliteration of the lumen.

The patient was continued on a full hepatic regimen and seen at intervals of one to seven weeks. Deep mahogany jaundice, marked pruritus and acholic stools continued, though the patient maintained a good appetite and an excellent morale. By November 10, 1948, the liver edge was palpable 5.0 cm. below the costal margin and extended across the epigastrium, the spleen was felt 2.0 cm. below the left costal margin, and ascites and leg edema were present. Laboratory investigation at this time revealed icterus index to be 1,024 units (serum diluted 640 times); Quick prothrombin test showed no coagulation in four hours; total serum proteins, 5.6 gm./100 c.c., with 2.55 gm./100 c.c. albumin and 3.05 gm./100 c.c. globulin; MCV, 127 cubic microns; MCH, 31.6 micrograms; MCHC, 24.8 per cent. Intramuscular vitamin K three times weekly reduced the Quick prothrombin time to 20 minutes. The patient left the state the latter part of December, 1948, but was recalled approximately seven weeks later because a Longmire operation to reëstablish biliary continuity was under consideration. However, by the time she returned her condition had deteriorated beyond recall and operative intervention was considered hazardous and inadvisable. The patient's condition remained relatively static until April, 1949, when she began to go downward rapidly. She died at home of a massive gastrointestinal hemorrhage on April 11, 1949.

The patient died 14 months after her original cholecystectomy and appearance of jaundice, and 12 months after the catheterization of the bile ducts. It is estimated that this patient lived 13 months after complete obstruction of her bile ducts had occurred.

Post mortem was performed about two and one-half hours after the patient's death and after the arterial embalming had been done. The body was that of an emaciated while female of 63; skin was mahogany colored. The abdomen was distended and, on opening it, a large amount of yellow, bile-stained fluid escaped. The peritoneal sur-

faces were slightly thickened. The organs were all normal in size and shape and location but were all deeply bile stained. The liver was perhaps slightly enlarged. There were adhesions on its anterior surface to the anterior abdominal wall in the intercostal area. There was a large amount of scar tissue in the area of the hilum of the liver. The gall-bladder was absent. The stomach and intestines contained a fairly large amount of dark red semifluid and clotted blood. After the duodenum was opened, pressure on the pancreas caused a small amount of fluid to escape through the ampulla of Vater. No bile ducts could be found in the scar tissue from the ampulla of Vater up to the liver. The liver was deeply bile stained and not abnormal in size, except possibly slightly enlarged. The weight was not obtained. The peritoneal surface was smooth, although there was slight thickening of the capsule. On cross section, tremendously dilated areas, which contained a large amount of clear fluid with a small amount of mucus, were opened. It was felt that these represented cystic dilatations of the intrahepatic bile ducts.

Report of microscopic examination was as follows:

The sections of the liver tissue showed the lobular pattern to be somewhat distorted, due to the presence of mild nodular regenerative changes. In the lobules a large amount of bile pigment was found. Some of this was within the cytoplasm of the Kupffer cells, while other masses of pigment were noted within the distended canaliculi. There were some degenerative changes, especially atrophy, in the central portions of the liver lobules and around the periphery surrounding the portal spaces. In the periportal area there was considerable fibroblastic proliferation, with extensive lymphocytic and occasional polymorphonuclear infiltration. Small bile ducts were numerous in this tissue, indicating proliferative and regenerative changes. Some of the smaller bile ducts were found to be distended and to contain bile pigment.

In another section of liver the same changes in the parenchyma were found as noted above, but in this section there was found a portion of a large bile duct which was greatly distended and surrounded by dense fibrous tissue.

In the sections of pancreas focal areas of fat necrosis involving the interlobular adipose tissue were found. These were relatively early, having polymorphonuclear infiltration and edema in the surrounding tissue. The lobules of the pancreas were fairly well preserved, except that in some areas the fat necrosis had extended into the parenchyma of this organ. There were some interstitial fibrosis and edema. There was a moderate lymphocytic and occasional polymorphonuclear infiltration of this interstitial fibrous stroma. In one of the larger pancreatic ducts the lumen was found filled with inspissated secretion containing polymorphonuclears. Small ducts in the pancreas also contained polymorphonuclears and fibrin deposits.

The sections of the spleen showed the capsule somewhat thickened, due to fibrosis. The splenic sinuses were markedly engorged with blood, and the pulp cords were thickened due to reticulum cell hyperplasia. There was moderate excess of hemosiderin pigment throughout the splenic pulp. The splenic corpuscles were quite small.

The sections of kidney showed extensive acute tubular degeneration. This consisted of dilatation of the proximal convoluted tubules, which were filled with an eosinophilic debris. The epithelial cells themselves had a cloudy granular eosinophilic cytoplasm. In some portions of the tubules, especially the distal convoluted and in the loops of Henle, there were some regenerative changes. The glomeruli were hyperemic but otherwise normal. Scattered throughout the renal tubules numerous bile pigment casts were found occupying the lumens. In some of the tubules, also, the lining epithelium was heavily pigmented with bilirubin. This involved the proximal convoluted tubules. In the collecting tubules also, bile pigment casts and some pigmentation of the epithelial cells could be made out.

Pathologic Findings: Marked obstructive and infectious biliary cirrhosis, chronic passive hyperemia of spleen, subacute interstitial pancreatitis with pancreatic fat necrosis and marked bile nephrosis.

Comment

Obliterative stenosis of the bile ducts is mentioned more frequently in the surgical than in the medical literature, undoubtedly because operative trauma repeatedly has been classified as the most common cause of benign biliary stricture.[2, 3, 4, 5, 6, 7] Cattell,[3] in a report of 123 patients operated on for benign strictures of the biliary tract (congenital strictures excluded), recorded the following approximate etiologic frequencies: operative injury, 80 per cent; cholangitis, 9 per cent, fibrosis of ampulla, 7 per cent; adhesions, 1.6 per cent, and external trauma, 0.8 per cent. Lahey [7] in 1937 felt that, for all practical purposes, strictures of the common and hepatic ducts were man-made. He stated that, though reports of complete obliteration of the extrahepatic bile ducts by diffuse inflammatory changes had appeared in the literature, the condition seemed to be quite rare. Wilson [5] also thought that obliterative cholangitis of all the extrahepatic bile ducts was rare.

Miller [6] felt that an inflammatory lesion which resulted in fibrosis of the wall of the common bile duct with diffuse stricture formation was not a common occurrence, and that it was a separate and distinct lesion from congenital strictures or strictures due to gall-stones or trauma.

Sowles [8] states that Judd [9] in 1926 expressed the opinion that the etiologic factor of operative trauma was sometimes overrated, and that many of the so-called traumatic strictures of the bile ducts were really due to an obliterative cholangitis. Judd [9] found that in 16 of 64 operations for stricture the condition was due to obliterative cholangitis, and that in 15 more of the 64 the condition might have been the result of obliterative cholangitis. Sowles [8] recounts two cases described by Ransom and Nichols, of Ann Arbor. The first was that of a 35 year old male with symptoms of a biliary calculus of seven weeks' duration in whom, at operation (there had been no previous surgery), extensive fibrosis and extreme narrowing of the lumen of all the extrahepatic bile ducts were found. Their second case was that of a 53 year old female who had had repeated attacks of chills, fever and abdominal pain for one year following a cholecystectomy for gall-stones. Jaundice had been present for one month prior to her second operation, which revealed both hepatic and common bile ducts to be tiny fibrous cords throughout their entire lengths, and which could not be probed or utilized for any type of anastomosis. Sowles further describes a case reported by Whipple of a 50 year old jaundiced woman in whom, at exploration, were found a collapsed gall-bladder, fibrous common and hepatic ducts and biliary cirrhosis. Nothing of a remedial nature was done, and yet the inflammatory process and stenosis subsided nine days after surgery, and the patient went on to recovery.

Walters [4, 10] noted that in an occasional case obliterative cholangitis may be the cause of stricture of the common bile duct. In 92 cases of strictures of the common and hepatic ducts, Walters and Lewis [11] observed 18 in whom the entire extrahepatic biliary passages were involved by the strictures.

Hagyard [12] reported two cases of chronic obliterative cholangitis, both oc-

curring following cholecystectomies, one of which was complicated by a biliary fistula. Flickinger and Masson [13] reported that at the Mayo Clinic, in the 10 year period 1933 through 1942, of 188 cases operated upon for benign stricture of the bile ducts, 22 cases (or 12 per cent) showed an extensive obliteration of the extrahepatic biliary system.

Graham [14] recorded a case of inflammatory obliterative cholangitis following cholecystectomy. In this case, five separate biliary reconstructive procedures were done. In the same paper, Graham mentions the personal communication of a 30 year old Puerto Rican who had had no previous surgery, who was jaundiced, and in whom at operation sclerosis of the common duct and part of the cystic and hepatic ducts was found.

Wilson [8] stated that strictures due to operative trauma or to ulceration from a stone are usually local in character, while those due to a chronic inflammatory process are more widespread. Eliot [15] also remarked that strictures due to septic cholangitis usually diffusely involve the greater part of both common and hepatic ducts. Lahey [7] reported a series of nine traumatic strictures of the biliary ducts, in seven of which there was dilatation of the duct above the stricture. Graham [14] thinks this proximal dilation of the duct in traumatic stricture is of diagnostic significance, since inflammatory strictures show no such proximal dilatation.

The mode of production of the diffuse inflammatory lesion of the biliary ducts walls is debatable. That operative trauma is not essential seems confirmed in view of the number of cases reported in which no previous surgery had been done. Ascending biliary infection originating in the intestinal tract has prompted Cole [16] to guard especially against this in biliary enterostomy. An infection beginning as a duodenitis and ascending the pancreatic and common bile ducts has been suggested by Strauss et al.[17] as the mode of production of lower common bile duct obstruction, biliary stasis, jaundice and, ultimately, liver cell breakdown and cirrhosis. Adams remarked that preëxisting cholecystic disease might be a causative factor in production of obliterative cholangitis, since the veins and lymphatics of the gall-bladder communicate directly with the liver and bile ducts; he cites Ranson and Malcolm as stating that infection ordinarily affects the gall-gladder first, while the ducts present marked ability to resist infection. Flickinger and Masson [13] suggested the possibility of obliterative cholangitis resulting from too vigorous curettage of the mucosa of the common bile duct in the performance of choledochotomy. Judd [18] felt that one of the main factors favoring chronicity of bile duct infection was the multiplicity of poorly drained sacculi in the mucosa of the whole biliary tree.

It is believed in our case that, even though a traumatic stricture was present and further duct trauma was incurred by catheterization at the second operation, the cholangitis was present even at that time and would have progressed to obliteration of the extrahepatic biliary system. This view is supported by the fact that at no time after closure of the initial biliary fistula was bile found in the extrahepatic duct system.

Summary

A case is recorded of chronic obliterative cholangitis occurring after an "easy" cholecystectomy in a 62 year old woman who lived for 13 months after

complete and permanent bile duct obstruction developed. Literature on the occurrence, frequency and mode of production of chronic obliterative cholangitis is reviewed.

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AMEBOMA OF THE TRANSVERSE COLON*

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THERE have been some scattered reports in the literature of ameboma of the colon, most of them in the foreign literature.[1, 2, 3, 4, 5, 6, 7, 8, 9] Only a few cases of ameboma of the transverse colon have been reported.[10, 11]

In Asia, hygiene and sanitation are at a somewhat primitive level. Parasitic infestation has always been a problem. Amebiasis, although found throughout the world, is more prevalent in these areas. Because of military operations in

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Korea, an increase in the incidence of amebiasis in our armed forces and in the veteran may be expected. It follows naturally, then, that amebic hepatitis, amebic liver abscess and ameboma may be seen more frequently.

Many new drugs and antibiotic agents have been developed since World War II. Chloroquine diphosphate,[12] bismuth glycolylarsanilate,[14] conessine,[15] aureomycin,[16] bacitracin [17] and terramycin,[18, 19] among others, have shown antiamebic

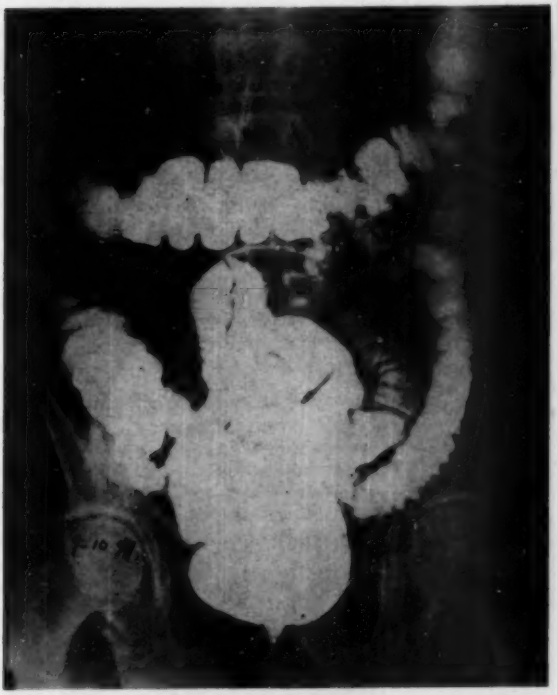

FIG. 1. July 10, 1947. There is a persistent area of narrowing, about 3 cm. long, in the distal portion of the transverse colon. The area of narrowing is well demarcated, with shelflike appearance at both ends. The narrowed segment is about 2 cm. wide and shows persistent coarse filling defect. There is no decrease in mobility of the segment and little delay in passing of the barium fluid.

activity. If the good results, as shown in the preliminary reports, stand the test of time, it may be that the treatment of amebiasis will be revolutionized. The use of emetine, chiniofon, diodoquin and carbarsone may be relegated to use in the occasional case in which the former drugs were without effect. Much was done in the past war to eliminate malaria as a major factor of medical disability in the theater of operations. This was accomplished by the routine (prophylactic) use of atabrine. It may well be that a similar regimen could be instituted by giving

an antibiotic or other drug to the troops in highly endemic regions for the prevention or amelioration of the diarrheal diseases and amebiasis.

From a clinical viewpoint, the differential diagnosis of amebic granuloma (ameboma) from other colonic conditions is extremely important, because these localized amebic lesions should be treated medically, whereas the other common localized growths in the colon require surgery. Furthermore, the morbidity and the mortality rates following surgery in ameboma have been high. If this con-

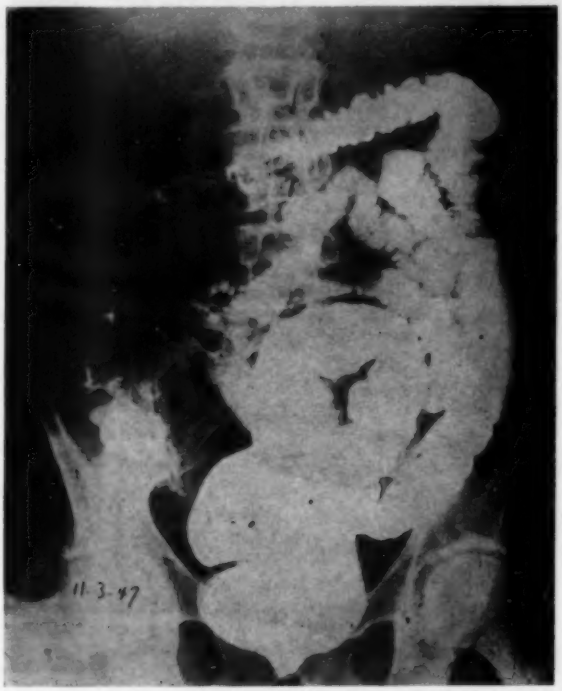

FIG. 2. November 3, 1947. There is no delay in passage of barium through the region of the resection in the transverse colon. There is only slight narrowing of the lumen at the site of the anastomosis.

dition is not recognized and the patient is operated upon, amebic peritonitis or amebic infection of the skin and subcutaneous tissues may ensue.[8, 20] The latter may cause extensive sloughing.

The history may be misleading. The patient may not recall any previous attack of diarrhea and, for that matter, may not have resided in a highly endemic region. The symptoms consist of localized abdominal pain and rapid emaciation. Nausea, vomiting and signs of chronic intestinal obstruction occur in the later stages. A palpable tumor is usually present, and multiple tumors may be found.

In the cecal region no tumor can be palpated,[21] and signs of acute intestinal obstruction may be the earliest manifestation. An ameboma may simulate a number of other organic conditions, such as an appendiceal abscess, carcinoma or hyperplastic tuberculosis of the colon. The presence of amebae in the stools may be difficult or impossible to demonstrate.

The site of the lesion in order of frequency is first in the cecum, then in the sigmoid and then in the descending colon. After chronic amebic ulceration has existed for some time, development of the granulomatous mass occurs. Partial obstruction may result. Peristalsis may cause acute intussusception with complete occlusion.

The significant roentgenographic findings are:[21, 22]

1. An amebic lesion may show multiple involvement, while a carcinomatous lesion is usually single.

2. Amebic obstruction of the colon is relatively incomplete, and we rarely, if ever, see an obstructive ileus. Because of this relatively incomplete obstruction, the passage of barium through the colon causes comparatively little pain. On the other hand, in carcinoma of the colon there is a rigid wall with more complete obstruction of the lumen of the large bowel which, when filled, almost always causes pain.

3. In amebiasis, the colic and pericolic inflammatory process usually involves a rather large segment of the colon, while carcinoma involves only a relatively small area of the intestine.

4. The transition from pathologic bowel to normal intestine in ameboma occurs gradually, with no spur formation; whereas, in carcinoma, there is an abrupt change from the pathologic to the normal bowel.

5. Since the bowel wall in ameboma is not completely rigid, the lumen will appear wider on maximal filling of the bowel and narrower after evacuation of the enema. There is thus a change in the caliber of the bowel lumen on the immediate and the postevacuation films.

6. The mucosal pattern of the involved portion of the colon is more regular in amebiasis than it is in carcinoma.

7. Following antiamebic therapy, the lesion usually shows prompt regression and the colon is more or less normal in appearance, so that it is difficult to determine the site of the previous lesion on follow-up roentgen studies.

Case Report *

A 54 year old white male crane operator was admitted to Cushing Veterans Administration Hospital, Framingham, Massachusetts, June 24, 1947, and was discharged April 26, 1948, after a stay of 278 days.

He complained of weakness, easy fatigability, anorexia and a weight loss of 24 pounds of one year's duration. He also complained of shortness of breath and orthopnea. Nine months previously he had been hospitalized in another institution, where a gastrointestinal series and a barium enema were done. No abnormalities were noted. After leaving that hospital he developed sharp stabbing pain in the left shoulder, and later a sensation of numbness in the left arm and hand. Six weeks before admission he noticed the onset of a "sick feeling," consisting of weakness, dizziness and perspiration, lasting five or 10 minutes and relieved by rest. The attacks

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occurred mainly on a change of position from lying to standing. It was noted in the past history that the patient was a World War I veteran who saw no overseas duty. In 1921–24 he had had severe epigastric pain, occurring at night and radiating through to the back. These pains were unrelieved by food or soda. A laparotomy was performed in 1924, and the patient thought a cholecystectomy was also performed. He had been a periodic drinker, consuming large quantities of alcohol for a period of one to two weeks and then abstaining for several months.

Physical examination revealed a poorly nourished male appearing depressed, tired and chronically ill. Ophthalmoscopic examination revealed moderate arteriosclerotic changes. The lungs showed the breath sounds to be diminished, with rhonchi and prolonged expirations at both bases, especially on the right. Blood pressure was 120/82 mm. of Hg; pulse rate, 80. The testes were atrophic. The prostate gland was moderately enlarged. There was a moderate kyphosis. Moderate varicosities of the legs were noted.

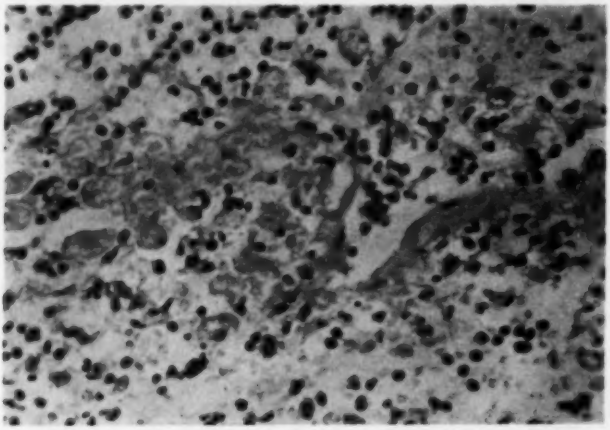

FIG. 3. Section through an ulcer, showing infiltration by polymorphonuclears, eosinophils and *E. histolytica*.

Admission laboratory findings revealed red blood cells, 3,800,000; hemoglobin, 11.8 gm.; white blood cells, 5,500, with a polymorphonuclear count of 61 per cent. Urinalysis was negative. The stools were positive for blood. Fasting blood sugar was 126. Electrocardiographic tracing was normal.

The patient was put on a high caloric diet but, because he did not gain weight very readily, further studies were instituted. A barium enema showed a lesion in the transverse colon (Dr. D. Kornblum) which was compatible with an early carcinoma.

On July 21, 1947, a laparotomy (Dr. Welch) was performed. The transverse colon showed an area of reddening and thickening, measuring about 8 cm. in length, about 6 inches proximal to the splenic flexure, most marked at the mesenteric border. There was no dilatation either proximal or distal to the lesion. There was no regional adenopathy. The bowel was not opened. A resection of the transverse colon was then performed, some 6 inches distal to the hepatic flexure up to the splenic flexure. The ends were reunited by an end-to-end anastomosis. The patient's postoperative course was uneventful. He ran a low-grade temperature for three days. The path-

ologist described the specimen as showing marked inflammatory change, with invasion of the coats of the colon by *Endamoeba histolytica*. The patient was then questioned regarding a history of amebiasis, but there was no known exposure. He recalled several bouts of diarrhea, lasting from six to 18 hours each, following alcoholic intake over a period of 25 years. Several smears from the rectum and warm stools were examined but no amebae could be recovered. Most of the stools showed *Giardia lamblia*. He was immediately placed on emetine therapy, gr. 1 daily for seven days, followed by a course of Diodoquin, carbarsone and Diodoquin again, each for 10 days. He was given atabrine for the infestation with *G. lamblia*. A repeat barium enema, in November, showed only a slight area of constriction at the site of the anastomosis. The patient had no further trouble from the lesion in the colon.

During the same hospitalization (December, 1947), he developed burning epigastric pain. A gastrointestinal series revealed a gastric ulcer, which was treated conservatively. On subsequent admission to the hospital, because of recurrence of gastric symptoms, a subtotal gastrectomy was performed. Following this he developed intestinal obstruction, which required surgical relief. Since then, he has had symptoms simulating "dumping syndrome."

The complete pathologic report (Dr. Robert Fienberg) reads as follows:

Gross: This was an opened segment of large bowel, 17 cm. in length and 6 to 7 cm. in circumference. Near one end was a flat, irregular, ill-defined ulcer in the mucosa, occupying an area of 4 cm. in diameter. Within the ulcer were irregular opaque yellowish patches and a granular reddish patch. On section, the wall at the base of the ulcer was thickened about 0.8 cm., as compared to a normal thickness of 0.4 cm. The markings here were ill-defined, although the layers could still be made out. Firm nodular fibrous tissue was noted on the mesentery, which measured 1 cm. in thickness at the base of the ulcer. Six lymph nodes from the vicinity of the tumor were firm and composed of homogeneous yellowish white tissue.

Microscopic: There were multiple ulcers in various stages of activity. Large active ulcers were covered by a thick layer of neutrophils and eosinophils. Within the exudate a few amebae were noted, containing nuclei characteristic of *Endamoeba histolytica* and ingested red cells. Most of the amebae were found in the tissues at the edges of the active ulcers. Beneath the exudate was a broad zone of hyalinized connective tissue which extended deep into the muscularis. Scattered lymphocytes and eosinophils and a few neutrophils were seen within the connective tissues. The muscularis below was similarly infiltrated. The serosa was fibrotic and thickened with the same infiltration. There was undermining of the adjacent mucosa. Beneath the adjacent intact mucosa the submucosa was infiltrated with lymphocytes, lymphoid follicles, scattered eosinophils and plasma cells. Less active ulcers were lined with granulation tissue, and proliferating epithelium covered the peripheral portion. Still other ulcers showed little sign of activity and were covered by a flattened layer of epithelium. The lymph nodes were hyperplastic and surrounded by fibrous tissue.

The Army Medical Museum confirmed the diagnosis of amebic involvement of the colon.

Comment

There are several points in this case which are of interest. There was no definite history of exposure to amebiasis, but this should not be too surprising, because amebiasis is worldwide in distribution. Towse, Berberian and Dennis,[53] in a recent survey in Albany, New York, found an incidence of over 10 per cent in a random sampling among chemists, technicians, laborers, medical students and patients who were asymptomatic or whose symptoms were not suggestive of amebiasis. Our patient had a chronic paroxysmal ambulatory diarrhea which was

not too incapacitating and which was brought to light only on direct questioning. He thought it was due to his excessive alcoholic consumption. Many investigators in the past have shown that alcoholism does aggravate amebic diarrhea.[24] Amebiasis has been found to be a cause of chronic illness with or without diarrhea, and at times patients of this type have been called psychoneurotics. This patient had had vague symptoms for many years. Even after the diagnosis was made, no amebae could be demonstrated in the stools. It has been stated that the best procedure in making a diagnosis of amebiasis and its complications is first to be amebiasis conscious. Then several stool examinations should be performed by a capable technician. It is worth while to bear in mind that negative stools may be misleading and that amebae may appear only at intervals. A complement fixation test for amebiasis might have been helpful in this case, as shown by Craig [24] and Strong.[25] In any suspicious case having bizarre symptoms and atypical roentgenographic findings of carcinoma of the colon, where immediate surgery (for intestinal obstruction) is not indicated, it may be worth while to delay operation for a short time and treat the individual for amebiasis. Repeat barium enema may show astounding improvement in a short period of time, as demonstrated by the report of Read and Nushan.[10]

Summary

1. A case of ameboma of the transverse colon has been presented.

2. The significant roentgenographic findings of ameboma have been discussed, together with the differential diagnosis from carcinoma of the colon.

3. This case further emphasizes the importance in lesions of the colon of being "amebiasis conscious."

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HYPERTHYROIDISM ASSOCIATED WITH DIABETES INSIPIDUS: RELIEF OF BOTH DISEASES AFTER TREATMENT WITH RADIOACTIVE IODINE * †

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Although diabetes insipidus was first recognized in 1674 by Thomas Willis, who noted the "insipid" taste of this urine when compared to the sweet urine of diabetes mellitus, the condition is rare, or at least infrequent. Futcher was able to find only 19 cases in the first 53,012 patients admitted to The Johns Hopkins Hospital. Only seven examples in 45,658 admissions to the Harriet Lane Home could be found in children under 12 years of age. Rowntree collected 127 instances of the disease from 800,000 admissions representing many hospital populations.[1]

Traditionally, the cases have been divided into two groups: (1) idiopathic, in which no cause for the symptoms could be found, and (2) secondary, in which the disease was secondary to a demonstrable process in or near the pituitary gland or diencephalon. The first group contains a considerable number of patients in whom a familial or hereditary factor can be established.

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† The I^{131} was supplied on allocation by the U. S. Atomic Energy Commission.

The second includes such diverse lesions as tumor, primary or metastatic, syphilis, skull trauma, a bullet lodged in the sella turcica, epidemic encephalitis, meningitis, bony disease of the base of the skull, and others too numerous to detail.

A mild polyuria and polydipsia are not infrequent in hyperthyroidism and have been noted often in the older literature, as well as more recently. The association of true diabetes insipidus and hyperthyroidism, however, is extremely rare and has many interesting aspects, because of the fact that both the thyroid gland and the pituitary-diencephalic area are involved in our present concepts of water metabolism and renal secretion.

We have had the unique opportunity of studying a young man in whom these two conditions existed simultaneously, and were able to observe the effects of control of his hyperthyroidism with radioactive iodine on the diabetes insipidus.

Case Report

The patient was a 32 year old white married salesman. He stated that for as long as he could remember, and certainly for the past eight years, he had suffered from great thirst and passed large amounts of water-clear urine. He would often drink a quart of liquid at a time, and passed urine as frequently as 10 times during the day and six times at night. On several occasions when he measured his urinary output it approximated "10 quarts in 24 hours." In other respects his past history was negative and there was no family history of polyuria. For the past two years he had become aware of heat intolerance, marked perspiration, palpitation, nervousness, asthenia and a progressive weight loss of 20 pounds.

He was admitted to the Mount Sinai Hospital on January 26, 1950. Physical examination revealed a nervous, tense, well developed white male with rapid, explosive speech. There was a slight bilateral lid lag, but no exophthalmos or extra-ocular muscle weakness. The ocular fundi were normal. The mucous membranes of the mouth and pharynx were dry. The thyroid gland was moderately and diffusely enlarged. No bruit was present over the thyroid. The lungs were clear. The heart was not enlarged; its action was regular, and the rate was 120 beats per minute. The blood pressure was 150/60–30 mm. of Hg, and the pulses were of the Corrigan type. The abdomen was normal. The skin was soft, supple and moist. There was a fine tremor of the outstretched fingers. The laboratory findings were as follows: The blood Wassermann test was negative. Blood sugar was 120 mg. per cent; blood cholesterol, 225 mg. per cent; cholesterol esters, 170 mg. per cent. Alkaline phosphatase was 16 and 12 King Armstrong units. Bilirubin was 0.4 mg. per cent, and the van den Bergh was negative. Blood proteins were 6.1 gm. per cent. A blood count gave the following results: hemoglobin, 15.7 gm.; red blood cells, 5,300,000; white blood cells, 7,600; polymorphonuclears, 74 per cent; lymphocytes, 18 per cent; monocytes, 6 per cent; eosinophils, 2 per cent. X-rays of the chest, skull, hands and feet were normal. The sella turcica was normal. The visual fields were normal for color and form. The electrocardiogram was normal. The arm-to-lung (ether) circulation time was 5.5 seconds, and the arm-to-tongue (Decholin) time was 10.5 seconds.

Data on Urine: The daily output of urine averaged 11 L., passed in 14 voidings, and the specific gravity varied between 1.001 and 1.005. Tests for albumin and sugar were negative. The sediment was unremarkable. When given 1 c.c. of Pitressin subcutaneously (20 u.), the patient's urinary output dropped to 3,400 c.c. in 24 hours.

He was studied by Dr. J. Sirota with special reference to his polyuria, with the following results:

Condition		Urine Flow c.c. per min.	Urine Creatinine conc. mg./100 c.c.
Four hours' water deprivation	Patient	4.0–5.0	40
	Normal	1.0	
1,600 c.c. water orally	Patient	9.0	13
	Normal	Slight increase, short lived	
12.5 gm. NaCl intravenously	Patient	13.0	8
	Normal	Decrease	
20 u. (1 c.c.) Pitressin, subcut.	Patient	1.8	89.0
	Normal	Some decrease	
Glomerular filtration rate	Patient	150 c.c.	
	Normal	150 c.c.	

These findings are typical of true diabetes insipidus.

Data on Thyroid Status: Basal metabolic rate, plus 72 per cent. Protein-bound plasma iodine, 23.1 gamma per cent (normal, 4 to 8 gamma per cent). Patient excreted 18 per cent of an oral tracer dose of 100 microcuries of radioactive iodine in 24 hours in a urine volume of 8,000 c.c. This finding is consistent with the diagnosis of hyperthyroidism.

Treatment: Patient was treated with 5.0 millicuries of radioactive iodine by mouth on February 3, and was discharged from the hospital on February 4.

Subsequent Course: Seen again on March 13, he was somewhat improved; he had gained seven pounds in weight and was less nervous and much quieter. His blood pressure was 122/82 mm. of Hg, and his pulse rate was 96 per minute. His basal metabolic rate was plus 11 on April 1. On May 1 the patient remarked that he was less thirsty and was voiding less frequently. A measured 24 hour urine output was now only 4,000 c.c. and was passed in seven voidings, as compared to the average of 14 voidings and 11,000 c.c. before treatment with I^{131}. On another occasion he passed 3,500 c.c., with specific gravities varying between 1.001 and 1.016. On November 12 he weighed 201 pounds, his basal metabolic rate was plus 4, and his total 24 hour urine output was 1,900 c.c., passed in six voidings, with specific gravities between 1.008 and 1.016.

Discussion

The pathogenesis of diabetes insipidus has been the subject of much speculation and experiment since its earliest description, already referred to, and the demonstration in 1913 by von den Velden and by Farini that the administration of an extract of the posterior lobe of the pituitary gland effectively controls the polyuria and the polydipsia. Previous to this, in 1906, Schafer and Herring had shown that the intravenous injection of this extract in anesthetized animals had led to a diuresis. This was the basis for a concept which held sway for some time that diabetes insipidus was a manifestation of increased posterior pituitary function, another example of the danger of transferring experimental observations on animals to humans without critique.

To Farini belongs the credit for first formulating the idea that a decreased function of the posterior lobe was the essential element in the polyuria of diabetes insipidus. The remarkable control of the polyuria by the subcutaneous, and later intranasal, use of posterior pituitary extract adds strong weight to

such a concept. In 1909 Coronedi [2] demonstrated that thyroidectomy in dogs led to a significant oliguria, which was not helped by the usual diuretics but which yielded promptly to thyroid extract. Eppinger [3] in 1917 elaborated this concept of the diuretic function of the thyroid hormone, and it was later employed extensively by Epstein in the management of the edema of lipoid nephrosis.

As early as 1918 von Hann [4] suggested, on the basis of postmortem material, that an intact anterior lobe of the hypophysis was necessary for the development of the syndrome of diabetes insipidus. This observation was confirmed by Rowntree, who reported that whenever the lesion in diabetes insipidus was limited to one lobe of the pituitary, that lobe was always the posterior and never the anterior.

Although posterior pituitary involvement came to be generally accepted as important in the polyuria under discussion, Camus and Roussy [5] in 1920 and Bailey and Bremer [6] in 1921 called attention to the importance of lesions in the diencephalon. They could establish (1) that total hypophysectomy without midbrain injury did not cause polyuria; (2) that isolated lesions in the tuber cinereum with no injury to the pituitary gland did produce polyuria, and (3) that polyuria could be produced by injury to the tuber cinereum in animals previously hypophysectomized without the development of polyuria. This work has been elaborated by Fisher, Ingram and Ranson [7] and their school, who have shown that any bilateral injury to the hypothalamic-hypophyseal tracts causes a permanent polyuria, and that this is reduced but not abolished by thyroidectomy and is restored by thyroid extract. It is probably not unfair to state that the present concept of diabetes insipidus is that it is the result of decreased function of the posterior pituitary lobe, which may be due to lesions of that lobe or of the tracts leading to it from the midbrain, and that an intact anterior pituitary lobe and a functioning thyroid gland are probably necessary for the full development of the syndrome. Further support for this concept is found in the work of Starling and Verney,[8] who showed that the kidney in a heart-lung-kidney preparation secreted a urine with the characteristics of that found in diabetes insipidus, but that a normal urine was secreted by this preparation when an isolated head was added to the system or when posterior pituitary extracts were added to the perfusion fluid.

Clinicians had adduced interesting and illuminating observations on the relation of the thyroid gland to diabetes insipidus. In 1920 Strauss [9] reported the spontaneous disappearance of diabetes insipidus in a patient who developed myxedema. McConnell,[10] McPhedran,[11] and Findley,[12] as well as Blotner and Cutler,[13] recorded cases of diabetes insipidus who were helped by thyroidectomy, either total or partial. Ferro-Luzzi [14] failed to observe any improvement in the polyuria after total thyroidectomy.

The case that we have reported is unique in several respects. It is the first in which modern methods of diagnosis of both the hyperthyroidism and the diabetes insipidus have been applied. The protein-bound blood iodine was markedly increased and the radioactive iodine tracer studies were typical of hyperthyroidism. The studies of renal physiology revealed the classic findings of true diabetes insipidus, namely, a normal filtration rate, an increased urine flow after water deprivation for four hours, a prolonged diuresis after oral

ingestion of water, an increased rather than a decreased urine flow after hypertonic saline administered intravenously, and prompt reduction of urine flow to normal after Pitressin.

The control of hyperthyroidism by radioactive iodine is so well established now that no further comment is necessary on this observation. The simultaneous control of the diabetes insipidus is most interesting, and adds weight to the experimental data that in some way the effects on water metabolism of the secretion of the thyroid gland are related to the syndrome of diabetes insipidus as it is seen clinically.

In view of the ease with which myxedema can now be induced in euthyroid subjects by radioactive iodine, one should consider this form of therapy in severe diabetes insipidus if one is convinced that the myxedema would be less troublesome than the polyuria.

Summary

A case of long standing diabetes insipidus complicated by hyperthyroidism of two years' duration was studied with modern methods for evaluating renal and thyroid function. The hyperthyroidism was controlled with one dose of radioactive iodine. This resulted in complete amelioration of both his thyroid disease and his diabetes insipidus. The physiologic implications of these observations are discussed.

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THE TOXIC EFFECTS OF HEXAETHYLTETRAPHOSPHATE IN MAN: A CASE REPORT*

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HEXAETHYLTETRAPHOSPHATE (HETP) is one of several organic phosphate insecticides which have been finding wide agricultural use since their development by the Germans during World War II. HETP is a heavy, yellow, syrupy liquid, miscible with water and readily absorbed in dangerous amounts through the skin, the gastrointestinal tract and the pulmonary system. It consists of a mixture of phosphoric acid esters, the principal insecticidal fraction being 15 to 20 per cent tetraethylpyrophosphate (TEPP).[1] HETP is manufactured under a variety of brand names and is used in water solutions as a spray. The related compounds, TEPP (a similar ester mixture containing about 40 per cent tetraethylpyrophosphate)[1] and parathion (o, o-diethyl o-p-nitrophenyl thiophosphate), are replacing HETP commercially because of their greater insecticidal potency. Several case reports of human intoxication and death from the organic phosphorus compounds have appeared in recent years.[2-4] Comprehensive chemical, toxicologic and pharmacologic studies soon followed.[1, 5-17] It was shown that the principal physiologic action in mammals is cholinergic (parasympathetic) stimulation mediated through inhibition of tissue and plasma cholinesterase enzymes. Muscarinic effects on the eye (miosis, difficulty in accommodation to distant vision), heart (slowing of conduction, bradycardia), gastrointestinal tract (anorexia, vomiting, diarrhea, cramping pain), lungs (bronchial constriction and hypersecretion), salivary, sweat and lacrimal glands (stimulation), and peripheral vessels (flushing) have been described.[1, 5, 6-8, 12, 15, 17] Nicotinic effects (muscle fasciculation, weakness) have led to the successful clinical use of the drugs in myasthenia gravis.[17-20] Central nervous system responses to HETP are varied and include giddiness, "nervousness" and slow waves in the electroencephalographic tracing.[1, 17, 21] For very complete pharmacologic discussions, the reader is referred especially to the papers of Grob[4, 16, 17] and Rohwer.[1]

The hazards to workers handling this new and potent group of chemicals are emphasized by the many papers describing protective clothing, breathing equipment and decontamination technics, and by the warnings issued by industrial hygiene agencies, agricultural journals and manufacturers.[22-28] The following report describes a severe, nonfatal poisoning of a worker exposed to a spray of aqueous solution of hexaethyltetraphosphate marketed under the brand name "Vapotone."† In this case, a direct irritative effect on the bronchial mucous membrane seems to have complicated the expected cholinergic signs and symptoms. I am indebted to Dr. William I. Coldwell for summarizing the records of the Southwestern General Hospital, El Paso, Texas.

* Received for publication December 2, 1950.

The opinions and assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

† California Spray Chemical Corporation, Richmond, California.

Case Report

A 55 year old male gardener was first seen at the dispensary (Navy Dispensary, White Sands Proving Ground, Las Cruces, New Mexico) on May 26, 1949, complaining of sharp pain in the left chest radiating to the left side of the neck, "tightness" and constriction of the chest, difficulty in breathing, cough, increased salivation, and voluminous whitish sputum which was foamy and occasionally blood streaked. He had first noticed malaise, anorexia, dyspnea, sweating and headache shortly after work May 24. He went to bed without eating his evening meal and did not feel like getting up for work the next day. He remained in bed, and in the afternoon began to have chest pain and a productive cough. He ate little, and felt progressively worse during that night and the next day. On admission at 3 p.m. on May 26 he was markedly dyspneic and appeared seriously ill. The blood pressure was 110/70 mm. Hg, pulse 104, temperature 102° F. and respirations 40 per minute. The lips and nail beds were cyanotic; the skin was moist and hot. The heart sounds were inaudible. The white blood count was 21,000 per cu. mm. A chest x-ray film showed somè opacity in the left lung base. A presumptive diagnosis of pulmonary infarction, left lower lobe, was made, and initial treatment consisted of atropine, morphine, penicillin and oxygen by nasal catheter. Morphine and atropine doses were repeated as needed during the night of May 26, but the patient continued to be dyspneic and to produce large amounts of thick, tenacious sputum. He was transferred to Southwestern General Hospital, El Paso, Texas, on May 27. The initial findings on hospitalization were: temperature, 100.2° F.; pulse, 110, regular and weak; blood pressure, 124/92 mm. Hg; respirations, 30 per minute, shallow, labored and regular. The patient appeared acutely ill. He was markedly dyspneic, and had cyanotic lips and nail beds. He complained of pain in the left chest anteriorly on coughing and on deep inspiration. He was well nourished, well developed and appeared to be about the stated age. The skin was warm and dry. There was some dried mucus in the nasal passages. The mouth and throat were dry and somewhat hyperemic. The neck was normal, without masses or rigidity. The accessory respiratory muscles were in very vigorous use. Dullness to percussion was found in the lower left chest. Many sonorous and sibilant râles could be heard over the front and back of the left chest, more marked in the lower portions. Over the left base posteriorly, moist crepitant râles and a definite friction rub were heard. The varied respiratory sounds made the cardiac sounds almost inaudible. The abdomen was soft and obese and without palpable viscera or masses. The prostate gland was slightly enlarged but smooth, freely movable and of normal consistency. There was no abnormality of the extremities. Homan's sign was negative, and there was no evidence of peripheral vascular disease. The neurologic examination was negative. The admission diagnosis of pulmonary infarction was used as the basis for immediate treatment. The patient was placed in an oxygen tent and continued on morphine and atropine therapy. In addition, he was given crystalline penicillin, 100,000 units every three hours, streptomycin, 1/8 gm. every three hours, papaverine, 3 gr. by mouth three times daily, heparin in Pitkin menstruum, 300 mg. intramuscularly, and Dicumarol, 300 mg. orally.

On the second hospital day the clotting time was six minutes and the prothrombin time 30 per cent of normal. The white cell count was 11,600 per cu. mm., with 65 per cent polymorphonuclear segmented cells, 4 per cent stab cells, 30 per cent lymphocytes and 1 per cent monocytes. The red cell count was 4,750,000 per cu. mm., hemoglobin, 95 per cent, 913.9 gm.; sedimentation rate (Sahli), 55 mm. per hour. Kahn and Kline serologic tests were negative. Non-protein nitrogen was 45 mg. per cent, and the blood sugar 115 mg. per cent. The urine samples obtained the first two hospital days were dark in color, but no red blood cells, casts, albumin or sugar were

found. There were occasional white blood cells and epithelial cells in the centrifuged specimens. Sputum examination for pathogenic organisms and abnormal cells was negative. Roentgenologic studies of May 28 were reported as follows: "The bronchovascular markings are prominent. There is marked pulmonary congestion with nodular consolidation in the left lower lobe. The right diaphragm is free. There is fixation on the left. The heart shadow is normal in size, outline and position. The diagnosis is localized nodular infiltration, left lower lobe, prominent bronchovascular markings, and pleurisy, left base." An electrocardiogram on the same day was reported within the limits of normal in all three limb leads and Leads V_{1-6}. The rate was 90 per second, P-R interval 0.18 second, and QRS 0.06 second. A sinus rhythm was present.

By the time the above studies were completed, the patient had improved sufficiently to permit amplification of the history. He described recent exposures to large inhaled doses of a spray insecticide of unknown chemical composition. The diagnosis was changed to chemical pneumonitis, and anticoagulant therapy was stopped. The temperature dropped on the second hospital day to 99.4° F., and by the sixth day he was afebrile. Roentgenologic study of the chest made June 2 was reported in these words: "There is a streak of atelectasis across the upper portion of the left lower lobe resulting from a recent, localized area of consolidation. Air filling of the lobe below this level is somewhat diminished. The diaphragm is free on the left. There is slight fixation at the right costophrenic angle. The bronchovascular markings are prominent. There is a solitary calcification at the right apex. The heart shadow is normal in size, outline, and position. Diagnosis: atelectasis left base."

The patient was discharged on June 5, after 11 hospital days, at which time he still had a moderately productive cough, and coarse rhonchi could be heard throughout the left lung field. On June 18 the patient felt well but complained of cough and wheezing on exertion. A few râles persisted in the left base. On August 27 he was seen for the last follow-up visit, with the same complaints of occasional bouts of coughing and wheezing.

A more detailed history of the patient was made on his return to work. There were no previous episodes of cardiac or vascular disease. He had suffered over several years from intermittent attacks of "bronchitis," marked by morning cough and sputum. He had also had numerous attacks of allergic rhinitis, and had used various histamine antagonist drugs for relief of nasal and conjunctival congestion. He customarily took several ounces of whiskey daily, and on weekends often greatly exceeded this quantity.

For several days prior to the onset of his first symptoms he had been spraying flower beds with "Vapotone," using a power sprayer. He had followed the instructions on the container to the extent of using a mask. He wore a shirt buttoned at the wrist and open at the collar. The hands, neck, eyes and most of the face were unprotected. He worked alone until the afternoon of May 24, 1949, when, for several hours, he and two assistants worked together spraying trees. None of the men on this occasion used any protective clothing, goggles or breathing equipment. The two helpers tried to stay "up-wind" from the clouds of spray, but the patient, who was operating the nozzle, did not take such precaution. No special attention was paid to decontamination after work, other than the usual washing of the hands and face. In the early evening and during the following day, all three workers complained of severe headache, malaise, nausea and anorexia. The patient seemed to be the most seriously affected, and was the only one who stayed in bed. By the time he sought medical aid, on May 26, the others had become asymptomatic.

Discussion

The patient described, and two fellow workers, were exposed to an aqueous solution of hexaethyltetraphosphate spray. The symptoms in all three can be ascribed to the known effects of the organic phosphate anticholinesterase compounds. The muscarinic features in the individual most seriously affected were nausea and anorexia, rapidly succeeded by increased bronchial secretion and dyspnea. As pulmonary edema increased, cyanosis became evident. Some degree of bronchial obstruction probably occurred in the left lung. Increased salivation and cough accompanied the production of a foamy white sputum. Nicotinic and central nervous system effects were not demonstrated, probably because of the time interval between exposure and first examination of the patient. Early evaluation of red blood cell and plasma cholinesterase activity was likewise impossible. The preliminary diagnosis of pulmonary infarction seems to have been in error.

In this patient the dose appears to have been accumulated over several days by at least one and probably several of the possible absorption routes (cutaneous, ingestion, inhalation). The patient became ill after a last large inhalation dose. The most prominent and prolonged effects were in the lung. In addition to the anticholinesterase actions of the chemical, it appears also to have been directly irritative to the bronchial mucous membrane. In this regard, it is most interesting to note that after an asymptomatic period of about 10 months, the patient developed a cough and pain over the lower ribs bilaterally. Bronchoscopy revealed a neoplasm of the right main bronchus, which was shown microscopically to be an undifferentiated carcinoma.

This case again emphasizes the dangers of the organic phosphate insecticides and the importance of adequate protective equipment for workers applying them. It also demonstrates the possibility of serious error in the diagnosis of inhalation poisoning. The carcinogenic potentialities of HETP are unknown.

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ACUTE NONSPECIFIC PERICARDITIS COMPLICATED BY THE DEVELOPMENT OF A FIBROUS PERICARDIUM*

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THE clinical entity of acute nonspecific pericarditis has been clearly defined.[1, 2, 3] It is characterized by a history of an antecedent respiratory infection, followed after an interval of from several days to several weeks by the development

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of the signs and symptoms of pericarditis with effusion. These consist of paroxysmal substernal or precordial pains, usually severe, and usually aggravated by coughing, deep breathing or motion. In addition, one finds fever, leukocytosis, increased sedimentation rate and a pericardial friction rub. An associated pneumonitis or pleural effusion is not uncommon. There are characteristic electrocardiographic changes consisting of RS-T elevations and T wave lowering or inversion, and the x-ray shows evidence of enlargement of the cardiac shadow, with signs of effusion. The etiology is unknown, although, because of its frequent association with primary atypical pneumonia, a viral etiology has been suspected.[3] Specific treatment has not been established but, with a viral etiology being considered, Levy [3] suggested the use of aureomycin, and Taubenhaus [4] reported two cases treated with aureomycin with apparent prompt remissions. The differential diagnosis must exclude myocardial infarction, rheumatic fever, tuberculosis or purulent pericarditis. The course has been consistently benign, with no complications reported, although recurrences are common.

Constrictive pericarditis is, in the main, a disease of unknown etiology. In two follow-up studies by Harrison [5] and Harrington,[6] no known cause for the development of constrictive pericarditis could be discovered in 78 per cent and 79 per cent of the cases, respectively. The known cause in the remainder was tuberculosis, in all but one case, which was due to sepsis. In the unknown cases, a large group in both series indicated that preceding respiratory infections, pleurisy or pericarditis had occurred in the past.

The case presented here is one which I believe can be classified as recurrent acute nonspecific pericarditis. In addition, I consider that there is roentgenographic and electrokymographic evidence of a fibrous or adhesive pericarditis, and that this represents a complication of a disease previously reported as entirely benign. I wish to offer the suggestion that this may be considered a "midpoint" in the development of a constrictive pericarditis, and that acute nonspecific pericarditis be considered one of the precursors of this more serious disease.

Case Report

The patient, a 52 year old white male dentist, was hospitalized in January, 1943, in a U. S. Army hospital in the Southwest Pacific for an acute tonsillitis. About 10 days after admission, while convalescing, he had a sudden attack of severe substernal pain. A tentative diagnosis of acute myocardial infarction was made but, after further study, the diagnosis was changed to acute cardiac dilatation. He made an uneventful recovery and was discharged to active duty after three more weeks.

First Hospital Admission: The patient was admitted to the Mount Sinai Hospital on December 19, 1946, complaining of dyspnea and of severe sticking pain substernally and in both shoulders. Symptoms had begun 48 hours previously and had persisted to admission. Physical examination was essentially negative. Temperature was 101° F., and the white blood cells were 10,300, with 80 per cent segmented forms. An electrocardiogram was normal. An x-ray of the chest showed a patchy mottled peribronchial infiltration in the right base consistent with a diagnosis of bronchopneumonia. Treatment consisted of penicillin and sulfadiazine. The pain persisted for 48 hours, after which it completely disappeared. After 48 hours, the temperature was normal, and the white blood cells were 6,600, with 73 per cent segmented forms. He was discharged after six days with a diagnosis of bronchopneumonia and diaphragmatic pleurisy.

Second Hospital Admission: The patient was well until December 25, 1947, when he was re-admitted to the hospital with complaints of the sudden onset of chills, fever and malaise 48 hours prior to admission. Four hours before admission, he complained of severe anterior chest pain radiating to the right scapular area and right arm. A physician who saw the patient at home was of the opinion that he had suffered an acute myocardial infarction, and had administered morphine sulfate gr. ¼. The pain, however, had been only partially relieved at the time of admission. Physical examination was essentially negative. Blood pressure was 118 mm. Hg systolic and 80 mm. diastolic; temperature 101.2° F.; white blood cells, 12,000, and sedimentation rate, 30 (Wintrobe). In 72 hours the acute symptoms had subsided and the temperature had returned to normal. The pain, however, continued to recur for the next several months. It was severe and paroxysmal in nature and could be precipitated by a sudden change in position. An x-ray of the chest taken on the day following admission showed an infiltrative lesion in the left base, a right interlobar effusion, and a left pleuropericardial effusion. One week later, a repeat film showed disappearance of the infiltrate in the left base and of the right interlobar effusion, but indicated a triangular heart shadow interpreted as a pericardial effusion. An electrocardiogram taken 12 hours after admission was normal. In 72 hours, a repeat electrocardiogram showed S-T elevation in Leads I and II, with inversion of T_I. One week later the tracings were normal, and they remained so for the duration of his stay. Other than the episodes of pain, his course was uneventful. There was a gradual increase in the amount of pericardial fluid as seen in the x-ray, and then a gradual return to a normal-sized heart shadow at the time of his discharge, 10 weeks after admission. There was never any evidence of cardiac tamponade, his pulse and blood pressure remaining constant, and venous pressure determinations in the antecubital vein being 70 and 76 mm. of water on two occasions. A tuberculin test (1:1000 O. T.) was negative, and repeated sputum examinations were negative for acid-fast bacilli, fungi and cancer cells. Treatment consisted of penicillin for the first week of his illness and analgesics as required.

Third Hospital Admission: The patient was well until June 19, 1949, when he was again admitted to the hospital after a sudden onset of severe precordial pain, associated with hiccough and aggravated by deep breathing, beginning 24 hours before admission. The pain was so intense as to require morphine sulfate for relief. The course was similar to the previous one, with fever, leukocytosis and an elevated sedimentation rate on admission, all returning to normal within one week. There was again x-ray, fluoroscopic and electrocardiographic evidence of pericardial effusion, all of which were normal within several weeks. The pain persisted intermittently for four weeks before disappearing. When present, it was severe in character and often associated with hiccough. Treatment consisted of penicillin for the first week. Cobra venom was used unsuccessfully for the relief of pain. There was never any evidence of tamponade. This admission was complicated by a toxic psychosis due to bromism, which responded well to withdrawal of the drug and fluids.

Fourth Hospital Admission: The patient was re-admitted on November 21, 1949, with a history of right and left chest pain aggravated by respiration, of 72 hours' duration, and severe substernal pain of 12 hours' duration. Physical examination revealed dullness with diminished breath sounds at both bases; blood pressure, 116 mm. Hg systolic and 80 mm. diastolic; pulse, 86, and temperature, 100° F. An x-ray of the chest revealed a bilateral pleural effusion, more marked on the left. A left thoracentesis was performed and 500 c.c. of clear straw-colored fluid were withdrawn. The fluid was negative for cells, culture and guinea pig inoculation. The patient was treated with aureomycin (2 gm. daily) on this admission, with a complete disappearance of pain and temperature within 24 hours. The pleural fluid did

not recur and the heart shadow did not increase in size. There were no electrocardiographic changes. He was discharged after 13 days.

X-ray and fluoroscopy at this time indicated that the left heart border was fixed, irregular and immobile (figure 1), and electrokymography was performed to confirm this observation. Electrokymograms were recorded over the aortic knob and the

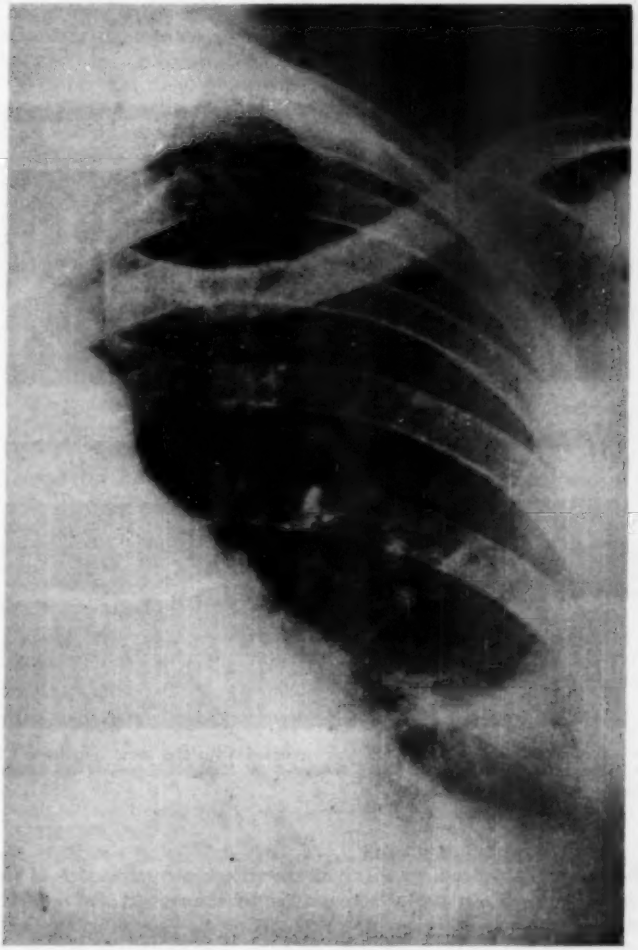

FIG. 1. X-ray showing the left heart border (November 21, 1949) characterized by fixed scalloped edges extending from the pulmonary conus down to the apex. Diminished density of the border zone formed by pericardial thickening.

left ventricular border. While the former tracing was practically normal, the latter failed to indicate any pulsation over an extensive area (figure 2). This was accepted as evidence that the contractility of the left ventricle was good but that the motion was masked by extensive adhesions. This interpretation fits with the studies of electrokymography in coronary heart disease by Luisada and Fleischner.[7] The abnormal type of tracing observed by Gillick [8] in constrictive pericarditis was not observed in this case. This was probably due to the different extension and severity of the lesions.

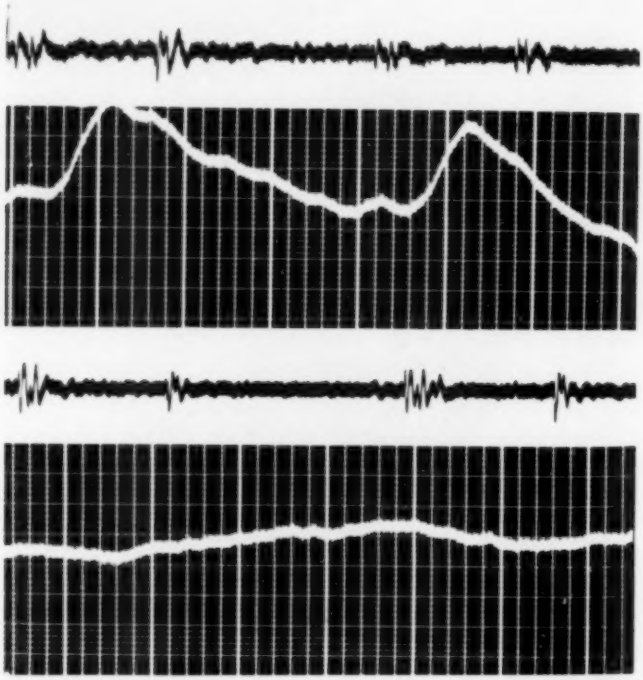

FIG. 2. Electrokymograms of the case recorded with the same amplitude. *Above*— border tracing of the aortic knob. *Below*— one of the border tracings of the left ventricle. Simultaneous phonocardiograms are above.

COMMENT

The case presented conforms with all the criteria for a diagnosis of recurrent acute nonspecific pericarditis. There is a history of an antecedent respiratory infection, with the classic signs and symptoms of the disease as previously described. I believe that the patient has had five episodes of the disease, the first two unrecognized. There has never been evidence of other cardiac disease, congestive failure, rheumatic fever or tuberculosis. In addition, this case shows evi-

dence of a fibrous or adhesive pericardium which, I suggest, may in time become constrictive.

Almost 80 per cent of cases of constrictive pericarditis are reported to be of unknown etiology. Since this case shows that the pericardium may become scarred with repeated episodes of acute nonspecific pericarditis, I believe that the latter should now be considered as one of the causes of constrictive pericarditis and should no longer be regarded as an entirely benign disease.

The etiology of acute nonspecific pericarditis is as yet undetermined and, as suggested by Levy,[3] probably diverse, with a virus or an allergic basis being most likely. Whether the development of constrictive pericarditis is dependent on the etiologic agent, the number of recurrences or the duration and severity of each attack must still be established. Because the fourth episode in the case described above was unusually severe, with pain persisting for four weeks, I believe that the latter may be the deciding factor.

Summary

1. A case is presented of acute nonspecific pericarditis with three definite and two probable episodes of the disease.

2. There is considered to be in this case definite roentgenographic and electrokymographic evidence of a fibrous or adhesive pericarditis.

3. It is believed that this represents the first reported complication of a disease previously considered benign.

4. It is suggested that this case represents a stage in the development of constrictive pericarditis, a disease reported to be of unknown etiology in almost 80 per cent of cases.

5. Aureomycin was apparently of value in treating the last recurrence of acute pericarditis.

Acknowledgment

I wish to express my gratitude to Dr. Aldo A. Luisada, Asst. Professor of Medicine and Program Director of Cardiology at the Chicago Medical School, for the taking and interpretation of the electrokymograms; and to Dr. Julian Arendt, Attending Radiologist at the Mount Sinai Hospital, for his assistance in the x-ray interpretation.

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AURICULAR FLUTTER WITH COMPLETE HEART BLOCK: "SADDLE EMBOLUS" IN A CASE OF RHEUMATIC VALVULAR DISEASE*

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The case recorded in this study presents unusual features in two respects: the special type of arrhythmia, and the occurrence of a severe embolism which was successfully operated upon. The various graphic studies and pharmacologic tests proved that the patient had auricular flutter with complete heart block. The coincidence of these two disturbances of rate and rhythm has been recently reviewed.[1, 2] Among the cases reported, only three were in young adults,[2, 3, 4] and two of them, like our case, were of rheumatic origin. The successful aortic embolectomy performed in our case also deserves to be reported, because only 23 such cases have been published so far.[5, 6, 7, 8, 10]

Case Report

A 46 year old white female was first observed on April 1, 1949, with a history of intermittent "fainting spells" of several months' duration. The patient had been told several years before that she had a "heart murmur." Past history was otherwise negative except for an appendectomy 25 years before.

Physical examination disclosed a pulse rate of 40 per minute which did not vary in successive observations. The blood pressure ranged from 240/100 to 210/80 mm. of Hg. No jugular pulsations were observed; no ankle edema was noted. The heart presented a mitral configuration on percussion; the apex was palpable in the sixth left interspace at the anterior axillary line; a systolic murmur and a diastolic rumble were heard over the apex, and an apical thrill was palpable at the same area. A soft systolic and a soft, blowing, early-diastolic murmur were audible over the aortic area and were transmitted to the vessels of the neck. There were no râles in the chest. The liver edge could be palpated two to three fingerbreadths below the right costal margin.

During the clinical course, several fainting episodes occurred similar to those in the Stokes-Adams syndrome. An electrocardiogram revealed the absence of P waves, the existence of tiny waves in diastole, and a regular ventricular rate (figure 1). There was a right axis shift, and evidence also of right ventricular strain (figure 1). The patient received ephedrine, desoxyn and adrenalin in oil initially. Later, it was found that capsules of ephedrine with amytal and aminophylline suppositories controlled the "fainting spells." These became infrequent and finally ceased. The clinical diagnosis was (1) rheumatic heart disease with mitral and aortic insufficiency and stenosis; (2) complete A-V block, and (3) auricular fibrillation or flutter.

On November 24 an acute emergency developed. The patient experienced precordial pain, then tingling of the legs which was rapidly followed by excruciating pain in the extremities. The pulsations of the dorsalis pedis arteries could be palpated on both sides, but the right leg was blanched and cool. The patient was given a subcutaneous injection of morphine and atropine and immediately hospitalized. On arrival, the blood pressure was 190/60 mm. of Hg, the pulse 32 and regular. The pupils were small and did not react to light. Four hours after the onset of the acute

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episode, the pulsation of the dorsalis pedis artery of the right side was barely palpable and the foot and leg were cold and clammy. A diagnosis of "embolus" of the right iliac artery was made. Because the patient was considered a poor surgical risk, surgery was deferred and medical treatment instituted.

Laboratory examinations revealed the following: *Blood:* red blood cells, 5,340,000; hemoglobin, 16.7 gm., or 107 per cent; white blood cells, 11,250. The differential count disclosed 3 stab cells, 71 segmented cells, 15 small lymphocytes and 11 monocytes. Slight anisocytosis was noted. *Urine:* specific gravity, 1.026; pH 5.5; albumin, 1 plus; white blood cells, 8 to 10; red blood cells, none; sugar, none; epithelial cells, many. Casts 2 to 3 per high power field. *Blood chemistry:* sugar 100; urea nitrogen 9.4. The prothrombin time was 15 seconds or 73 per cent of normal.

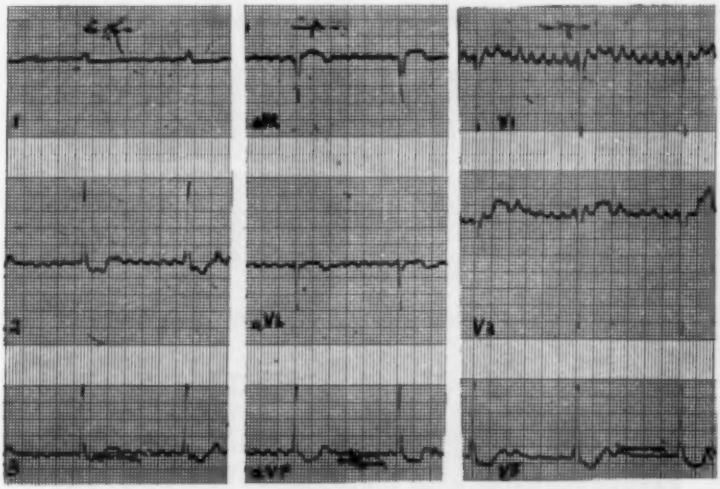

FIG. 1. Electrocardiogram (Poly-Viso Sanborn) in the three standard leads, the three augmented unipolar limb leads and three chest leads (V_1, V_5, V_6).

Twelve hours later, the abdomen was diffusely tender and rigid, and there was noted a mottled cyanosis of the right leg and blanching of the left foot. No oscillometric readings could be obtained on either side of the legs and thighs. A diagnosis of "saddle embolus" was made. This change for the worse was considered an indication for immediate surgery as the only possible life-saving procedure, and embolectomy was performed on November 25 under spinal anesthesia. Both iliac arteries were opened and the clots removed. There was a good reflux from the left iliac and a poor return from the right. The patient received 50 mg. of heparin before surgery and at six hour intervals thereafter while Dicumarol was begun. Heparin was discontinued when the prothrombin time was reduced to between 20 and 30 per cent of normal, and Dicumarol was continued. The same prothrombin level * was maintained subsequently for 11 months, with bi-weekly control, to prevent the occurrence of other embolic phenomena.

* The Dicumarol dosage was controlled by means of the Quick prothrombin test [15] according to the Link-Shapiro modification.[16]

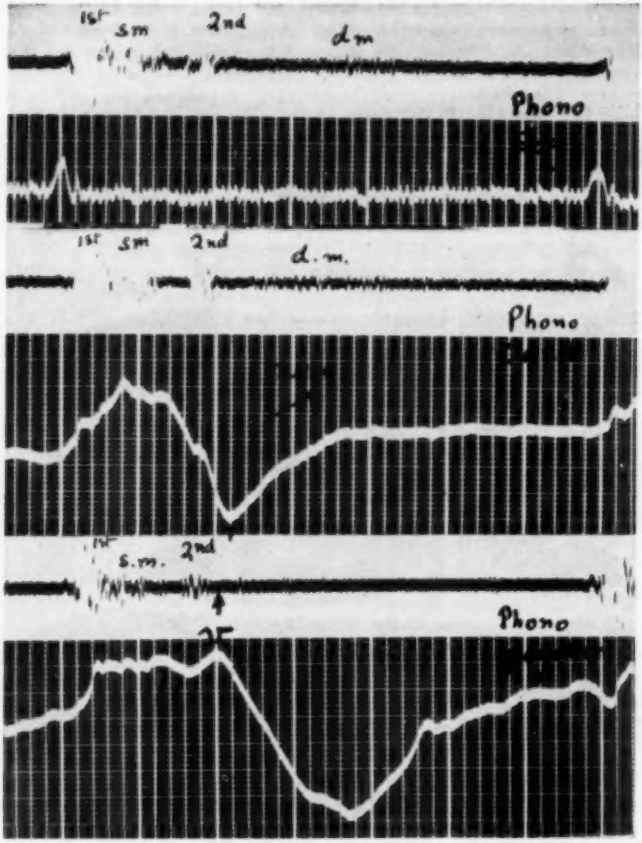

FIG. 2. A phonocardiogram at the apex presents both a systolic and a diastolic murmur. It is compared with: (a) The electrocardiogram (muscular tremor mars the baseline of this tracing). (b) The apical cardiogram. (c) The jugular tracing. The apical cardiogram shows a slow phase of filling in diastole, evidence of mitral stenosis. The jugular tracing has a plateau during ventricular systole, evidence of tricuspid regurgitation.

Twenty-four hours after surgery, the pulsations of the femoral arteries and the left popliteal pulse could be palpated. The left foot was cool but the color was good. The right foot, which could not be moved voluntarily, showed pallor and mottling and was cool to just below the knee. A right foot drop was present. There was a blue-black area 5 by 5 cm. on the lateral aspect of the right calf which gradually became leathery in consistency; no further change occurred. The pulse of the right dorsalis pedis could not be felt at any time after surgery, but despite this, the color of the foot remained good even though the leg continued to feel cool, and no new gangrenous patches developed.

During the hospital stay, a chest film was taken. It revealed an enlarged left auricle and "the possibility of a left auricular thrombus" (Dr. J. Arendt). To ascertain the cause of the slow pulse and to complete the cardiac study, electrocardiograms, phonocardiograms and mechanical tracings were taken and pharmacologic tests were performed.

The electrocardiograms were taken in the three standard leads, the augmented unipolar limb leads and six unipolar chest leads. A special bipolar lead (C2-C4) in the right interspace was also used, to obtain the best record of right auricular potentials. The electrocardiograms revealed a fixed ventricular rate of 50/min., associated with the existence of small and at times slightly irregular waves during diastole. The possibility of an auricular fibrillation was considered. However, the larger, regular auricular waves revealed by the chest leads and the recording of diastolic waves of auricular origin in the jugular tracing led to the diagnosis of auricular flutter with complete A-V block.

Atropine, 1 mg. intramuscularly, produced no change in the ventricular rate. Digitalization [17] (1.2 mg. digitoxin in three days, then 0.2 mg. daily) was followed by nausea, without change of either the ventricular rate or the electrocardiographic picture. Quinidine was also tried but the patient could not tolerate the drug. Compression of either the carotid sinus or the eyeballs left the ventricular rate unchanged.

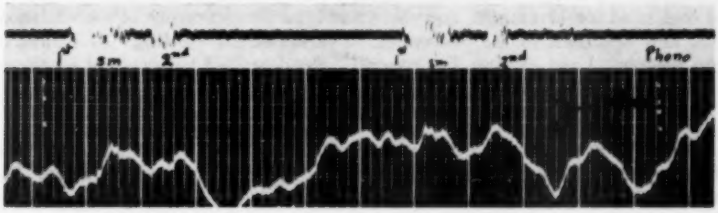

FIG. 3. Phonocardiogram and jugular tracing during convalescence. Multiple waves are present in the venous tracing, indicating auricular flutter.

Phonocardiograms and mechanical tracings (jugular, carotid, apical) were recorded (figures 2 and 3). The phonocardiograms confirmed the existence of mitral and aortic insufficiency and stenosis. The vibrations of a systolic murmur and a diastolic rumble were recorded over the apex and midprecordium. A diamond-shaped systolic murmur and a few early-diastolic vibrations were recorded over the aortic area. A jugular tracing revealed a systolic plateau, evidence of tricuspid regurgitation (figure 2). However, subsequent tracings were of normal appearance, so the regurgitation was attributed to functional tricuspid insufficiency.

The patient was discharged from the hospital on January 10, 1950, and was then followed as an out-patient.

DISCUSSION

Two main points in the clinical history of this case deserve special mention. The first is the existence of auricular flutter with complete A-V block. Among the cases recently reviewed in the literature, only three were in young people,[3, 4] and only two in cases of rheumatic heart disease.[3, 4] Our patient had hypertension. However, the existence of a mitral valvular lesion and the occurrence of embolism were considered as evidence of rheumatic heart disease, even in the

absence of any known attack of rheumatic fever. As this disease is frequently followed by damage of the myocardium in general and of the auricular myocardium in particular, the existence of auricular flutter and of an A-V block of a complete and permanent type can be easily explained.

Embolectomy for a "saddle embolus" of the aorta has been reported in a few cases.[5, 6, 7, 8] In our case, the operation was successful despite the long delay between the occurrence of the embolism and surgery (19 hours), and despite the existence of heart disease with valvular and myocardial damage.

Another point deserving mention concerns the use of anticoagulants. It has been stated that Dicumarol should never be given to a patient after surgical intervention.[9] On the other hand, six recent reports prove the feasibility of prolonged prophylactic anticoagulant therapy on an ambulatory basis (and despite surgical intervention).[10, 11, 12, 13, 14, 15]

Three possible approaches were considered to prevent recurrent embolization. The first was to terminate the auricular flutter by the use of digitalis or quinidine, or both. This was tried without success. The second was to resect surgically the left auricular appendage. The patient's general condition would not permit such a procedure. The third was based on a regimen of long-term continuous anticoagulant therapy. Dicumarol therapy was started at the time of surgery and continued for 11 months, and there has been no recurrence of embolization.

A new approach to the prevention of intravascular clotting,[9] by means of alpha tocopherol and calcium, has recently been described but was not employed in this case.

Summary

A case is presented of rheumatic heart disease with mitral and aortic insufficiency and stenosis, complete heart block and chronic auricular flutter. The patient had a "saddle embolus" which was successfullly treated by embolectomy 19 hours after its onset.

Prolonged prophylactic anticoagulant therapy with Dicumarol was employed to prevent any further embolization.

Acknowledgment

I wish to express my gratitude to Dr. A. A. Luisada, Program Director of Cardiology at the Chicago Medical School, for the graphic study of this case.

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EDITORIAL

THE PRESENT STATUS OF THERAPY IN ACUTE LEUKEMIA

After many years of fruitless investigation, from a therapeutic standpoint, of the etiology and control of acute leukemia, a small break in the completely dark horizon occurred in 1948 with the introduction of the folic acid antagonists.[1] This was followed, in 1950, by observations that the hormones ACTH and cortisone also exerted a temporary beneficial effect upon certain types of acute leukemia.[2] From the mass of literature which has accumulated in the past four years a few facts have emerged and become crystallized. It is quite apparent that these are but the veriest beginnings of an understanding of this inexorably fatal malady. Nevertheless, it may be useful at this time to attempt to assess and evaluate the current status of the problem.

In a recent review of studies on the etiology and nature of leukemia, Furth [3] concluded that the essential change in this disease resides in the leukemic cell and consists of an acquired inability of immature leukocytes to respond to forces normally regulating their proliferation and maturation. This change is essentially what is understood by the term neoplastic and may be due to manifold causes. Widely differing chemicals, hormones, and physical agents (x-rays, gamma rays, beta rays and slow and fast neutrons) can apparently produce the change. Although clear-cut evidence exists that virus-like agents can cause fowl leukemia, such is not yet the case for mammalian leukemia. Furth, however, points out that the control of a disease may be accomplished without knowledge of its cause.

The evaluation of any therapeutic measure must be geared to a knowledge of the natural history of the disease under consideration. Spontaneous remission in acute leukemia is quite rare. In a review of the literature through 1948, Dreyfus [4] was able to find only 21 reports of spontaneous remission in acute leukemia. Birge, Jenks and Davis [5] found only 11 cases reported during the period 1931–49. Diamond and Luhby [6] in a review of 300 cases in children found 26 instances of spontaneous remission, but in only about one-half of these was the remission complete. Spontaneous remission in adults with acute leukemia is even rarer. Remissions are of brief duration with inevitable relapse and death. Although the factors respon-

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[3] Furth, J.: Recent studies on the etiology and nature of leukemia, Blood **6**: 964, 1951.

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[5] Birge, R. F., Jenks, A. L., and Davis, S. K.: Spontaneous remission in acute leukemia, J. A. M. A. **140**: 589, 1949.

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sible are completely unknown, attention has been repeatedly called to the fact that an infection of some sort has often preceded the remission. Bassen and Kohn [7] have called attention to the fact that a severe leukopenic state is frequently present just prior to the remission.

Sufficient data have now accumulated to demonstrate that the incidence of remissions following the use of various anti-folic acid compounds far exceeds that of spontaneous remission. In a series of 190 patients, Farber [8] noted a remission rate of 61 per cent. Twenty-seven of 43 patients studied by Heinle [9] underwent complete remission. Of 96 children with acute leukemia studied by Burchenal,[10] 32 or 33 per cent experienced complete remission. In a group of 21 children treated by the essayist, 13 complete remissions (62 per cent) were noted.[11] Similar experiences have been recorded by numerous other investigators.

The characteristics common to all of these studies can be readily summarized. With hardly any exception, high remission rates (50 to 60 per cent) have only been observed in children. Among adults a remission rate of approximately 3 to 5 per cent is the rule. Although many reports avoid morphologic classification, the observations of many competent investigators clearly indicate that it is the lymphatic variety of acute leukemia which is most responsive to therapy. This is, of course, the most common variety of acute leukemia in childhood. Yet in adults even this variety of leukemia responds very poorly or not at all. There is almost universal agreement that monocytic and myelogenous leukemia at any age are virtually unresponsive to therapy with the anti-folic acid compounds as well as ACTH and cortisone. No evidence exists yet to illuminate the cause of this differential response. Is it a function of age, cellular metabolism, or etiology?

The striking aspect of the complete remission in acute leukemia is the virtual disappearance of all evidences of the disease process. Both clinically and hematologically the patient appears well and is able to participate in all normal activities during this period. Most investigators have kept patients upon a daily maintenance dose of the anti-metabolite throughout the period of remission. The duration of remission varies considerably. Many workers have now followed individual patients who have survived for periods of 24 to 27 months. A statistical analysis of survival time would perhaps not give nearly so favorable a picture. In a group of 17 patients, analyzed by Bierman et al.,[12] who were treated only with transfusions and antibiotics

[7] Bassen, F. A., and Kohn, J. L.: Multiple spontaneous remissions in a child with acute leukemia: the occurrence of agranulocytosis and aplastic anemia in acute leukemia and their relationship to remissions, Blood **7**: 37, 1952.

[8] Farber, S.: Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood **7** (Supplement): 107, 1952.

[9] Heinle, R. W.: Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood **7** (Supplement): 113, 1952.

[10] Burchenal, J.: Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood **7** (Supplement): 115, 1952.

[11] Sacks, M. S.: Unpublished observations.

[12] Bierman, H. R., Cohen, P., McClelland, J. W., and Shimkin, M. B.: The effect of transfusions and antibiotics upon the duration of life in children with lymphogenous leukemia, J. Pediat. **37**: 455, 1950.

a mean survival time of 8.9 months was noted. Burchenal, in a review of cases of acute leukemia treated at Memorial Hospital during the period 1926–47, observed a mean survival time of four to five months. In a group of patients treated with anti-folic acid compounds the same investigator noted an average survival time of 16.9 months (range 7.5 to 27 months). From a long range point of view, one would venture the opinion that, at this stage, the nature of the remission is of greater importance than its duration.

The employment of ACTH and cortisone in acute leukemia has altered the therapeutic picture somewhat. The pattern of remissions is essentially the same as for the folic acid antagonists, i.e., the best responses have been observed in children with acute lymphatic leukemia. Furthermore, there is general agreement that remissions are of shorter duration. The mechanism of action of these hormones is, as yet, poorly understood. That it is apparently different from the anti-metabolites is indicated by the response of patients who have become resistant to the antagonists. The alternate use of both groups as needed, in individual cases, seems to be the common pattern at present.

The folic acid antagonists are extremely toxic and must be employed with great care and frequent clinical observation. The earliest manifestations of toxicity are gastrointestinal in nature. Ulcerative stomatitis is the earliest warning of impending overdosage. Following shortly upon this are anorexia, vague abdominal pain, and diarrhea. These are indications for prompt temporary discontinuance of therapy. Diffuse, partial alopecia is fairly common, but is not regarded as an indication for stopping treatment. The possible use of the citrovorum factor in combating toxicity will be discussed below. Although at least 22 compounds have been synthesized in the folic acid antagonist group, the drugs of choice have remained aminopterin and a-methopterin.[13]

What light has the use of the folic acid antagonists cast upon the nature of leukemia? An adequate appraisal of this question would necessitate a consideration of the rôle of folic acid in cellular metabolism which is beyond the scope of this brief essay. Suffice it to say that this vitamin appears to be essential for the synthesis of nucleoproteins being particularly needed in the formation of thymidine.[14] This biological property is especially important for rapid cell growth. Microbiological research led to the discovery that folic acid is converted in the body into a closely related compound which was found to be an essential metabolite for the organism *Leuconostoc citrovorum* and which was therefore called citrovorum factor (CF).[15] Nichol and Welch demonstrated that aminopterin inhibits the conversion of folic

[13] Williams, J. H.: Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia, Blood **7** (Supplement): 100, 1952.

[14] Jukes, T. H., Broquist, A. P., and Stokstad, E. R. L.: Vitamin B_{12} and "citrovorum factor" in the nutrition of *Lactobacillus leichmanii* and *Leuconostoc citrovorum*, Arch. Biochem. **26**: 157, 1950.

[15] Savberlich, H. E., and Baumann, C. A.: A factor required for the growth of *Leuconostoc citrovorum* 8081, J. Biol. Chem. **176**: 165, 1948.

acid to CF.[16] These and other experiments have led to the conclusion that the so-called folic acid antagonists are in reality citrovorum factor antagonists. Thus as much as 5,000 micrograms of folic acid daily were ineffective in combating the lethal effect of the daily administration of 25 micrograms of aminopterin to rats, whereas 100 micrograms of citrovorum factor daily were effective.[17] Leukemic cells and various embryonic tissues being geared to more active biosynthesis have a greater need for the citrovorum factor, or folinic acid, as it is also known. These cells, therefore, are more readily affected by the inhibition of CF by the antagonists. Bethell has recently reported studies which indicate that immature leukocytes contain relatively high folic acid concentrations.[18] These observations, although obviously incomplete, afford some insight into the metabolism of the leukemic cell and the rationale for the use of the anti-folic acid compounds.

Having once responded to therapy, what factors are responsible for the relapse of the leukemic process? Partial answers are available from the study of experimental mouse leukemia. Using mouse leukemia L 1210, Law transferred this strain through a series of animals who were receiving a folic acid antagonist and observed the development of a resistant strain.[19] As a matter of fact, not only did the leukemic cell become resistant, but it also seemed to develop a dependence upon the antagonist for optimal growth. These resistant cells retained their new character through 33 consecutive serial passages. Law felt that the cells had undergone a stable and irreversible heritable change. The cells, however, were still sensitive to other anti-leukemic compounds such as triethylene melamine. Quite similar observations have been made by Burchenal. The phenomenon of the development of resistance in the leukemic cell is apparently quite analogous to the development of bacterial resistance to antibiotics. It seems likely that the altered cell is able to use the antagonist, without first converting it to folic acid or CF, in the synthesis of nucleic acids. The tolerance appears to be confined to the leukemic cell since the host still continues to develop systemic symptoms of toxicity with overdosage of the drug.

Therapeutic progress in as tragic a disease as acute leukemia must, at times, seem incredibly slow. Yet even a brief survey of the researches in this field during the past four years seems to indicate that there is promise of greater insight into the nature and control of leukemia in the not-too-distant future.

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REVIEWS

The Auricular Arrhythmias. By Myron Prinzmetal, M.D., Eliot Corday, M.D., Isidor C. Brill, M.D., Robert W. Oblath, M.D., H. E. Kruger, M.D., and associate authors. 387 pages; 22 × 28.5 cm. Charles C. Thomas, Springfield, Ill. 1952. Price, $16.50.

Members of this auctorial team have already earned a reputation for unseating well established riders. In this text they record the ingenious investigations of the auricular arrhythmias that have occupied them for about four years. From the abundant and convincing evidence they have accumulated, the widely accepted and seldom disputed theory of circus movement must surely be abandoned, and their preliminary observations on the Wolff-Parkinson-White syndrome must cast serious doubt on the validity of the accessory bundle of Kent.

Their methods and equipment are as fascinating as their results. The high speed movie camera, capable of taking up to 3,000 frames per second, proved their most useful tool. When such films were then projected at as few as eight frames a second (i.e. slowed by over 300 times), events which occupied but a fleeting second in the heart itself required up to six minutes of leisurely observation on the screen. Thus the minutest details of auricular contraction were seen for the first time. Over 100,000 feet of film were studied in this way. Then the cathode-ray oscillograph especially enabled the electrographic deflections of auricular fibrillation to be greatly magnified and much more easily analyzed. A third valuable instrument was the multiple channel electrocardiograph which permitted three or four leads to be recorded simultaneously.

In experimental dogs the arrhythmias were produced by the local application of aconitine or by electrical stimulation of the auricle. Whenever the opportunity presented itself spontaneous and induced arrhythmias in patients were also investigated and invariably bore out the principles derived from animals.

The authors describe in turn their investigations on the normal auricles, the auricular premature beat, auricular tachycardia, flutter and fibrillation. One chapter is devoted to new criteria for interpreting the electrocardiograms of auricular disturbances. Further chapters deal with ventricular aberration, pharmacological considerations and treatment. In their final chapter the authors propound the "unitary nature" of the auricular arrhythmias and present their conclusion that all four arrhythmias have the common pathogenetic mechanism of an irritable ectopic focus; the particular arrhythmia resulting depends entirely on the rate of discharge from that focus. Thus they have confirmed by their more complete experiments and newer methods the conclusions of previous workers, such as Rothberger and Scherf, who had earlier denied the circus theory.

This is a work with which every cardiologist and internist should become familiar. Not only are the abnormal mechanics of the auricles elucidated, but considerable new light is shed on the normal function of these chambers. Further, in the light of these results, the whole question of digitalis and quinidine action must be reconsidered and reinvestigated. Another interesting feature is the authors' original and convincing analysis of flutter waves in the electrocardiogram, and to the interested follower the chapter on ventricular aberration and the Wolff-Parkinson-White syndrome reads like a detective story.

Against this background of excellence, criticisms are minor but deserve attention. Readability is marred by one major irritation—the lengthy legends for the most part merely recapitulate the description in the main text. The illustrations are of high

quality, and usually a glance at one of them is sufficient to drive home the point with great force and clarity; yet often description is presented in triplicate—in the text, in the legend and by labels on the illustration itself. This is probably an expression of the fear of being misunderstood which seems to haunt the authors, for throughout the text they tend to be overexplicit.

Footnotes have been said to be as disturbing to the reader as a fire alarm on the wedding night, and it is therefore a pity that the authors have included so many, most of which are of sufficient importance to have been incorporated in the body of the text. Another minor complaint is a noticeable disregard for the integrity of infinitives.

It is a great pity that in the chapter devoted to pharmacological considerations no distinction is drawn between strophanthin and digitalis. For it is largely to the unscientific pharmacological habit of using strophanthin experimentally and applying the results to "digitalis," that misconceptions concerning the clinical action of digitalis and its glycosides have arisen in the past. To assume that adequate dosage of strophanthin achieves the identical pharmacological ends as "digitalization" is, in the light of present knowledge, to assume too much.

None of these defects seriously detracts from this work which is a classic in many ways. Not only does it present a faithful record of brilliant investigations and ingenious technics—which must once and for all disprove a theory almost universally accepted for decades—but the publishers also have done the work masterly, if tardy, justice by their artistic efforts.

H. J. L. M.

Cardiac Emergencies and Heart Failure. By Arthur M. Master, M.D., Marvin Moser, M.D., and Harry L. Jaffe, M.D., The Mount Sinai Hospital, New York. 159 pages; 14 × 20.5 cm. Lea and Febiger, Philadelphia. 1952. Price, $3.00.

This monograph deals with the prompt diagnosis and treatment of cardiovascular emergencies. It lists the drugs needed for this purpose in the physician's bag. It concerns the arrhythmias, acute pulmonary edema, congestive heart failure, angina pectoris, coronary occlusion, coronary insufficiency, syncope, hypertensive crises, and other conditions. The occasional brief case presentation adds interest to the text. One wishes there were a better integrated, more complete discussion of the clinical differential diagnosis of the various arrhythmias. The reviewer can not agree that . . . "it is best to wait several hours before beginning drug therapy (in the paroxysmal tachycardias) except in cases where the patient is in shock or cardiac failure."

This small text can prove useful to the general practitioner for whom it is intended.

S. S.

Disorders of the Heart and Circulation. Edited by Robert L. Levy, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, and Attending Physician, Presbyterian Hospital, New York. 944 pages; 18.5 × 25.5 cm. Thomas Nelson and Sons, New York; available from the Williams and Wilkins Co., Baltimore. 1951. Price, $12.00.

This book consists of a collection of articles on heart disease by 41 authors, originally written as individual chapters for the Nelson System of Medicine. It covers most of the important aspects of cardiac disease. A compilation of articles such as this has certain advantages and disadvantages. The chief advantage is that, unlike a text by a single author, it can have different subjects presented by an authority in those fields. Thus, many of the chapters are excellent, particularly the one on the physiology of congenital heart disease by Richard J. Bing, and the one on hypertensive vas-

cular disease by George A. Perera and Dana W. Atchley. A disadvantage is the presence of overlapping, such as a chapter of 28 pages on chronic constrictive pericarditis by one author, and a thirteen page section on the same subject in the preceding chapter on diseases of the pericardium. This text is not encyclopedic. There seems to be no well-defined plan of arrangement of the chapters. It lacks a clear-cut planned approach to heart disease. It may therefore be recommended for certain of its chapters, but does not, despite its 944 pages, equal some other recent volumes as a comprehensive, well-organized text on diseases of the heart.

S. S.

Metabolic Interrelations: Transactions of the Third Conference, New York, N. Y., January 8–9, 1951. Edited by EDWARD C. REIFENSTEIN, JR., M.D. 294 pages; 15.5 × 23.5 cm. Sponsored by Josiah Macy, Jr. Foundation, New York. 1951. Price, $4.00.

This volume concerns the metabolism and structure of bone and serves to make available to the non-participants certain papers and subsequent discussions which took place at the Third Conference on Metabolic Interrelations in January of 1951 sponsored by the Macy Foundation. The material includes results obtained by newest technics such as histochemical studies with bone slices, studies of inductor substance in bone grafts, deposition and turnover of radioactive metals and electron micrography. The considerations concerning the rapidity of mobilization of bone calcium, the action of phosphatase, and the influence of various endocrine factors seem particularly relevant to clinical problems. While the reader is sometimes at a loss to follow discussion concerning items which seem to have been presented visually and not presented in the book, the lively and stimulating nature of the discussions is preserved to a great extent.

G. E. G.

A Pediatric Manual for Mothers: Questions and Answers on the Care and Feeding of Infants and Children. By HARRY A. LITCHFIELD, M.D., and LEON H. DEMBO, M.D. 269 pages; 13 × 18.5 cm. Grune and Stratton, New York. 1951. Price, $2.50.

The authors have used a question-and-answer format to present basic information regarding infant and child care to mothers. The advantages, according to the authors, is that a book of this type permits the mother to obtain rapid, pertinent information without extensive reading.

The material presented includes most of the problems which confront the parents of today, even a short section on "Baby Sitters." The practical nature of the book might be gathered from the following question-answer:

Q. Should a sitter be fed during her hours of "sitting"?
A. It is a good idea to have some sort of snack available. A hungry sitter is handicapped.

Also included are sections on Toys, Books, Movies, Radio, Comic Books and Television.

The authors have made a conscientious effort to exclude advice on treatment. The style of the book reflects throughout the extensive, practical pediatric experience of the authors.

Physicians may safely recommend this book to mothers, with the assurance that the mothers will find answers to many routine questions that formerly were asked of the physician.

J. E. B.

Callander's Surgical Anatomy. 3d Ed. By BARRY J. ANSON, M.A., Ph.D. (Med.Sc.), Professor of Anatomy, Northwestern University Medical School; and WALTER G. MADDOCK, M.S., M.D., F.A.C.S., Elcock Professor of Surgery, Northwestern University Medical School. 1074 pages; 18 × 26 cm. W. B. Saunders Company, Philadelphia. 1952. Price, $14.00.

The original edition of *Surgical Anatomy* fulfilled a need for a book in which anatomy and its surgical application were considered together or in close sequence.

This revised edition (third) retains the original pattern of presentation. Systems and organs are studied in relation to each other and fundamental surgical features are stressed rather than technics.

Revised portions of the book greatly enhance its value. Chapters on the Thoracic Cavity and Its Contents, and the Abdominal Cavity and Contents are particularly noteworthy.

This edition is splendidly illustrated. Many illustrations appearing in the previous edition have been replaced. The index, which includes illustrations as well as subject material, is most comprehensive.

The excellent presentation fulfills its primary purpose of fitting "the professional needs of the advanced student and the practitioner" extremely well.

G. H. Y.

Somatic and Psychiatric Treatment of Asthma. Edited by HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York; Assistant Professor of Physiology, The College of Physicians and Surgeons, Columbia University. 751 pages; 15.5 × 24 cm. The Williams and Wilkins Company, Baltimore. 1951. Price, $11.00.

This volume represents the collaboration of 34 authors under the editorship of Harold A. Abramson. It is divided into six parts: Basic Concepts, General Testing and Treatment, Nature of Inhalant Allergens and Their Therapy, Somatic Therapy, Psychotherapy, and Special Geography.

The defects and advantages of all such collaborative texts are found in this publication. The tempo is jerky and the merits of the different portions vary with the importance of the section and the literary ability of the contributor. On the whole, however, the book seems a definitely valuable addition to the allergic literature. The Physiology of Respiration, Lung Volume and Air Flow Characteristics in Asthma, The Psychodynamics of Respiration, The Influence of Experimental Neuroses on the Respiratory Function, The Nature of Pollen Allergens, and Aerosol Therapy of the Lungs and Bronchi are particularly good. The section "Psychotherapy" is stimulating but leaves one with the conviction that this form of therapy is more effectual in the practices of the authors than in the practices of physicians less enthusiastic and less well trained in this field of therapy.

"Special Geography" is interesting in that it reveals conditions demanding diagnostic and therapeutic measures foreign to our experience.

In the reviewer's opinion, the volume has advantages that far outweigh its defects and warrant its purchase by those physicians especially interested in the subject.

H. M. B.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Medicine and Surgery. From the Graduate School of Medicine of the University of Pennsylvania. 441 pages; 25.5 × 17 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $8.00.

Annual Review of Medicine. Volume III. WINDSOR C. CUTTING, Editor, Stanford University School of Medicine, and HENRY W. NEWMAN, Associate Editor, Stanford University School of Medicine. 442 pages; 23 × 15.5 cm. 1952. Annual Reviews, Inc., Stanford, California. Price, $6.00.

Anurie bei Chromoproteinurie. By PROF. DR. HANS U. ZOLLINGER. 138 pages; 21 × 14.5 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kart. DM 14.70.

Blood and Blood Derivatives Program. United States Civil Defense, Federal Civil Defense Administration (Technical Manual). 179 pages; 23.5 × 15 cm. (paper-bound). 1952. United States Government Printing Office. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington-25, D. C. Price, 40 cents.

Diseases of the Heart and Circulation. 2nd Ed. By ALBERT A. FITZGERALD PEEL, M.A., D.M. (Oxon.), F.R.F.P.S. (G.), Physician for Diseases of the Heart, Victoria Infirmary, Glasgow, etc. 472 pages; 22.5 × 14 cm. 1952. Oxford University Press, New York. Price, $7.50.

Gastrointestinal X-Ray Diagnosis. By MAX RITVO, M.D., Assistant Professor of Radiology, Harvard Medical School, etc.; and I. A. SHAUFFER, M.D., Instructor in Radiology, Harvard Medical School, etc. 838 pages; 26.5 × 18.5 cm. 1952. Lea & Febiger, Philadelphia. Price, $20.00.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 458 pages; 28.5 × 19.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Brosch. DM 89.-

Normal Blood Pressure and Hypertension: New Definitions. By ARTHUR M. MASTER, M.D., Cardiologist, The Mount Sinai Hospital, New York, etc.; CHARLES I. GARFIELD, M.D., Research Assistant in Cardiology, The Mount Sinai Hospital, New York, and MAX B. WALTERS, M.D., F.R.C.P. (Can.), Member, Heart Station, Vancouver General Hospital, Canada, etc. 144 pages; 24 × 15 cm. 1952. Lea & Febiger, Philadelphia. Price, $4.00.

The Origin of Life and the Evolution of Living Things: An Environmental Theory. By OLAN R. HYNDMAN, B.S., M.D., F.A.C.S. 648 pages; 23.5 × 15.5 cm. 1952. Philosophical Library, New York. Price, $8.75.

Physical Medicine in General Practice. 3d Ed. Edited by WILLIAM BIERMAN, M.D., and SIDNEY LIGHT, M.D.; with Twenty-two Contributors. 798 pages; 24.5 × 16.5 cm. 1952. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $12.50.

Principles of Human Physiology (Originally written by E. H. Starling, M.D., F.R.C.P., C.M.G., F.R.S.). 11th Ed. By SIR CHARLES LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. Birmingham, Emeritus Professor of Physiology in the University of London; with Chapters on the Special Senses by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Emeritus Professor of Physiology in the University of London. 1,210 pages; 24.5 × 16 cm. 1952. Lea & Febiger, Philadelphia. Price, $11.00.

Principles and Practice of Anesthesiology. By VINCENT J. COLLINS, M.D., Director of the Department of Anesthesiology at St. Vincent's Hospital of the City of New York. 528 pages; 24 × 15.5 cm. 1952. Lea & Febiger, Philadelphia. Price, $10.00.

Psychiatry and Medical Education: Report of the 1951 Conference on Psychiatric Education Held at Cornell University, Ithaca, New York, June 21–27, 1951. Organised and Conducted by the American Psychiatric Association and the Association of American Medical Colleges. Editorial Board: JOHN C. WHITEHORN, M.D., Chairman; CARLYLE JACOBSEN, Ph.D.; MAURICE LEVINE, M.D., and VERNON W. LIPPARD, M.D.; Editorial Assistants: STELLA BLOCH HANAU and ROBERT L. ROBINSON. 164 pages; 22.5 × 14.5 cm. 1952. American Psychiatric Association, Washington. Price, $1.00 (bound).

Reaction to Injury: Pathology for Students of Disease. Volume II. *The Reactions of Submission and Adaptation and the Disease Entities Arising out of Their Elaboration.* By WILEY D. FORBUS, M.D., Professor of Pathology, Duke University, etc. 1110 pages; 26 × 18 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $20.00.

Le Rétrécissement Mitral: Études Anatomiques, Cliniques et Thérapeutiques. By R. LUTEMBACHER. 304 pages; 26.5 × 19 cm. (paper-bound). 1950. Masson et Cie, Editeurs, Paris. Price, 1800 fr.

A Text-book of Pathology. 7th Ed. By E. T. BELL, M.D., Emeritus Professor of Pathology in the University of Minnesota, Minneapolis, Minn.; Contributors, B. J. CLAWSON, M.D., Emeritus Professor of Pathology in the University of Minnesota, and J. S. MCCARTNEY, M.D., Professor of Pathology in the University of Minnesota. 1,008 pages; 24 × 16 cm. 1952. Lea & Febiger, Philadelphia. Price, $12.00.

The Unipolar Electrocardiogram: A Clinical Interpretation. By JOSEPH M. BARKER, M.D., F.A.C.P., Cardiologist, Yater Clinic, etc.; Assisted by JOSEPH J. WALLACE, M.D., F.A.C.P.; Advised by WALLACE M. YATER, M.D., F.A.C.P.; Foreword by FRANK N. WILSON, M.D., F.A.C.P. 655 pages; 25.5 × 17 cm. 1952. Appleton-Century-Crofts, Inc., New York. Price, $12.50.

Vascular Diseases in Clinical Practice. 2nd Ed. By IRVING SHERWOOD WRIGHT, M.D., Professor of Clinical Medicine, Cornell University Medical College, etc. 552 pages; 21 × 14.5 cm. 1952. The Year Book Publishers, Chicago. Price, $8.50.

COLLEGE NEWS NOTES

New Life Members

The College is pleased to announce that the following Fellows have become Life Members since the publication of the last issue of this journal:

Dr. J. Thomas Hardesty, Long Beach, Calif.
Dr. Herbert W. Pohle, Milwaukee, Wis.
Dr. James M. McFadden, La Fayette, Ind.
Dr. Elwood Whittier Mason, Milwaukee, Wis.
Dr. Jerome G. Kaufman, Newark, N. J.
Dr. Earl Saxe, New York, N. Y.

A. C. P. Postgraduate Courses

The American College of Physicians through its Committee on Postgraduate Courses has adopted a program of eight courses during the autumn of 1952. The schedule includes a Course in Cardiology at Mount Sinai Hospital, New York, N. Y., under Dr. Arthur M. Master, F.A.C.P., and Dr. Charles K. Friedberg, F.A.C.P., September 30-October 4; a Course in Internal Medicine at the University of Pittsburgh School of Medicine under Dr. Roy R. Snowden, October 6–11; a Course in Cardiology at Emory University School of Medicine, Atlanta, under Dr. R. Bruce Logue, F.A.C.P., October 20–24; a Course in Hematology at the New England Center Hospital, Boston, under Dr. William Dameshek, F.A.C.P., November 10–15; a Course in Internal Medicine at the Presbyterian Hospital and the University of Illinois College of Medicine, Chicago, under Dr. Frank B. Kelly, F.A.C.P., November 17–21, this Course preceding the large Midwest Regional Meeting of the College at Chicago on November 22; a Course in Gastro-enterology at the University of Pennsylvania Graduate School of Medicine, Philadelphia, under Dr. Henry L. Bockus, F.A.C.P., December 1–6; a Course in Internal Medicine at the University of California School of Medicine, Medical Extension, San Francisco, under Dr. Stacy R. Mettier, F.A.C.P., and Dr. H. Clare Shepardson, F.A.C.P., December 8–12; and a Course in Internal Medicine at the Johns Hopkins and University of Maryland Medical Schools under Dr. Maurice C. Pincoffs, M.A.C.P., and Dr. A. McGehee Harvey, F.A.C.P., December 8–13.

The detailed Postgraduate Bulletin should be available by the time this notice appears in print, and may be obtained by writing to the Executive Secretary, American College of Physicians, Philadelphia 4, Pa. All Courses are limited as to maximal registration, and it is therefore important that members of the College file their applications early. Non-members having adequate background of training and experience for advanced work may be admitted to courses where facilities are adequate to accommodate them. The tuition fee to members will be $30.00 per course; to non-members, $60.00.

Research Fellowships Available Through the American College of Physicians for 1953–54

The American College of Physicians offers up to six Fellowships in medicine or in pediatrics for the term July 1, 1953–June 30, 1954. This program has been in operation since 1937, and many of the early Fellows under this program have become eminent in teaching, research and clinical practice. The Fellowships are designed to pro-

vide for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice, and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend varies from $3,000.00 to $4,000.00. Application forms may be obtained from the Executive Secretary, Mr. E. R. Loveland, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. Applications must be submitted, in duplicate, no later than October 1, 1952. Announcement of awards will be made during November, 1952.

The A. Blaine Brower Traveling Scholarships of the American College of Physicians

An Endowment Trust in the amount of $10,000.00 was established by Dr. A. Blaine Brower, F.A.C.P., a Regent of the College, in 1950. The initial program was so successful and these scholarships were in such demand that on November 12, 1950, the Board of Regents made an additional appropriation of $10,000.00 to this Fund, and provided that two Scholarships hereafter may be awarded annually.

The aim of these Scholarships is to provide an opportunity for worthy young physicians, preferably Associates of the College, to spend a month, more or less, as visiting Fellows at some institution or institutions for observation and postgraduate study. The Committee on Fellowships and Awards of the College can readily facilitate opportunities for this Fellowship at outstanding institutions where a month's observation, contact and study would be an exceptional inspiration and a practical source of training.

The Brower Scholars for 1952 were Dr. William H. Bates (Associate), Cottonwood, Arizona, and Dr. Daniel H. Labby (Associate), of the University of Oregon Medical School, Portland, Oregon. The Committee on Fellowships and Awards arranged a program for Dr. Bates, with the coöperation of Dr. Eugene Eppinger, F.A.C.P., of Boston, at the Peter Bent Brigham Hospital, Massachusetts General Hospital, Boston City Hospital, New England Deaconess Hospital and the New England Center Hospitals. Dr. Labby's program for one month was at the Peter Bent Brigham Hospital and the Massachusetts General Hospital in Boston, the New York Hospital and the Rockefeller Institute Laboratories in New York, and at the University of Michigan Medical School and Laboratories. Reports from the recipients indicate that they gained invaluable suggestions and ideas from the institutions they visited, refreshed themselves on the field of their particular interests, received inspiration from contacts and new acquaintanceships, emphasizing the exceeding value of this Traveling Scholarship program.

The income, approximately $400.00 each, is used for payment of the expenses, in whole or in part, of the recipient for attendance for a short period of time for observation and study at outstanding institutions of medical teaching, research or practice. Announcements of the availability of two Scholarships under this program for 1953 were mailed to all Associates of the College during July, and applications should be filed by October 15, 1952. Those who applied previously, but failed to receive an award, are not excluded from re-applying again.

A. C. P. Committee on Fellowships and Awards Meet at Ann Arbor

The Committee on Fellowships and Awards of the American College of Physicians met at the Simpson Memorial Institute of the University of Michigan, Ann Arbor, June 21, 1952, with the following in attendance: Dr. Cyrus C. Sturgis, Chairman, Dr. Douglas Donald (substituting for Dr. Charles A. Doan), Dr. William C. Menninger,

Dr. Wesley W. Spink, Dr. Wallace M. Yater, Dr. T. Grier Miller, President, Mr. E. R. Loveland, Executive Secretary, Dr. Benjamin G. Horning and Dr. M. R. Kinde, both of the W. K. Kellogg Foundation, Dr. E. Hugh Luckey of Cornell University and Miss P. M. Ott, Recording Secretary.

The Committee reviewed the program of the A. Blaine Brower Traveling Scholars for 1952, and expressed full satisfaction with the program to date.

The Committee received advice that Dr. James Edwin Wood, III, to whom a Research Fellowship was awarded for 1951–52, but who could not accept because of military duty, had informed the College that he has accepted a permanent appointment and will not in the future be interested in pursuing this Fellowship. Thus, the funds, $3,500.00, previously held in reserve for him, have been turned back to the Research Fellowship Reserve Fund.

The Committee discussed at length the matter of the closing date for receipt of applications for Research Fellowships, and held to the opinion that such applications must be received by October 1, for processing and action at the November meeting of the Board of Regents. The comparatively small number of applications, the Committee believes, is partially due to the uncertainty of young physicians with regard to the possibility of military duty, and to the fact that hospitals are trying to retain their residents for longer periods of time. The Committee reviewed at some length the matter of increased publicity concerning the College Research Fellowship Program. Presently notices are sent to the Deans of Medical Schools, Professors of Medicine, Professors of Pediatrics, and to a selected list of names furnished by the Chairman of the Committee. It was decided to make an announcement also to the Medical Directors or Superintendents of hospitals approved for residencies in medicine.

Applications for extension of Latin-American Fellowships from three of the present Fellows were considered and approved. The Committee reviewed the ten Latin-American Fellows selected in 1950, receiving the final reports from the preceptors in those cases for which final reports had not previously been received. The concluding dates of each Fellowship and the status of the issuance of certificates were reported. The Committee also reviewed the current programs of ten Latin-American Fellows who started in 1951. Interim reports were presented from the preceptors, and satisfactory progress was noted in every case.

New Applications of seventeen Latin-American Fellows were received, accepted, and initial programs determined upon. These candidates come from countries as follows: Brazil—1, Chile—5, Colombia—2, Costa Rica—1, Ecuador—1, El Salvador—1, Mexico—2, Paraguay—3, Uruguay—1. Those requiring further training in English were assigned to the English Language Institute of the University of Michigan for appropriate training; many thereafter will attend a special orientation course of from three to six months at Cornell University, and then they will pursue special training under preceptors selected by the College. In some instances the candidate may be assigned to formal graduate medical training at such institutions as the University of Pennsylvania Graduate School of Medicine.

The Committee determined that inasmuch as the United States Ambassadors usually conduct a formal ceremony in the home country of the candidate when his American diplomas are presented, the College in the future would deliver the certificates of Latin-American Fellows to the United States Ambassadors in their country so that these would be presented formally at ceremonies arranged by the respective Ambassadors.

The Committee had obtained numerous suggestions for recipients of the John Phillips Memorial Award and the James D. Bruce Memorial Award for 1953, and proceeded to select the special nominees to be submitted to the Executive Committee of the Board of Regents for approval.

The Committee reopened a discussion of the amount of the stipend offered by the College for its Research Fellows. A report on the stipends of comparable Fellowships by other organizations was presented and the Committee decided not to recommend any change in the present Research Fellowship stipend, believing that eventually, after the military situation has improved, an adequate number of candidates will be received.

Supplement to 1951 Directory, American College of Physicians

A Supplement to the 1951 Directory of the American College of Physicians is in course of publication and will be ready for distribution in early September. This Supplement will include additional elections to membership and changes in status of members since the publication of the 1951 Directory. The next complete Directory of the College will be published in 1953.

A. C. P. Investigating Group Insurance

At a meeting of the Board of Regents at Cleveland, April 25, 1952, the Board of Regents adopted a Resolution approving in principle the policy that the Board is interested in sponsoring group insurance, health and accident and/or professional liability, for its members, and directed that a full study of the subject be made by a duly appointed Committee. President T. Grier Miller appointed Dr. A. B. Brower, Dayton, Ohio, Chairman; and Dr. J. Owsley Manier, Nashville, Tennessee; and Dr. Walter B. Martin, Norfolk, Virginia, members of the Committee.

Recently many county medical societies, state medical societies and several national medical groups have initiated group insurance plans for health and accident, and one or more national societies have initiated a group plan for professional liability. The group plan provides marked reductions in premiums, and, if 50 per cent or more of the members subscribe, it becomes available to all members up to certain specified limits in age, without medical examination. The Executive Offices report progress on the investigation of various available plans, and believe the Committee on Insurance will present to the Board of Regents in November a proposal which will be superior to most plans previously adopted by medical groups and certainly inferior to none.

Coming Examinations by Certifying Boards

American Board of Internal Medicine, William A. Werrell, M.D., Secretary-Treasurer, 1 West Main St., Madison 3, Wis.

Oral Examinations—San Francisco, Calif., Sept. 3–6, 1952;
Philadelphia, Pa., Nov. 13–14, 1952;
Washington, D. C., Nov. 17–18, 1952.

Gifts to the College Library of Publications by Members

Dr. Joseph M. Barker, F.A.C.P., Washington, D. C., has presented to the College Library of Publications by Members an autographed copy of his book, *The Unipolar Electrocardiogram*, which has recently been published by Appleton-Century-Crofts.

Dr. Francis M. Pottenger, F.A.C.P., has also presented to the Library an autographed copy of his recent autobiography, *The Fight Against Tuberculosis*, published by Henry Schuman.

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College, and thus the library has become a living memorial to the member-authors.

Army Medical Service to Offer 17 Postgraduate Courses for Military and Civilian Doctors

The Army Medical Service will conduct 17 short postgraduate courses in surgery, psychiatry and other subjects of major medical importance during the latter half of 1952.

The instruction is open to both military and civilian physicians and is the broadest program of postgraduate professional training of this type ever sponsored by the Army Medical Service, according to Major General George E. Armstrong, MC, F.A.C.P., Army Surgeon General. The courses will be given at six large Army teaching hospitals and the Armed Forces Institute of Pathology in Washington, D. C.

Inquiries seeking detailed information should be addressed to Department of the Army, Office of the Surgeon General, Technical Information Office, Washington 25, D. C.

American Public Health Association to Meet in Cleveland

The 80th Annual Meeting of the American Public Health Association and the annual meetings of 38 related organizations will be held in the Public Auditorium, Cleveland, Ohio, October 20-24, 1952.

The subjects to be covered in the scientific program include: Tuberculosis, Virus Diseases, Professional Education, Hepatitis and Leptospirosis Infections, Interpreting Fluoridation Projects to the Community, Research in School Health, Group Methods in Public Health Programs, Nutrition Consultants and Nurses Work Together, Animal Diseases of Economic and Health Importance to Man, Home Care Programs, Role of the General Practitioner in Organizing Health Programs, Results of Chronic Disease Programs, Industrial Medical Services, Food Processing and Sanitation, The Nutritional Survey in Program Planning, The Social Environment in Health and Disease, Use of Audio-Visual Aids, Critiques of Recent School Health Publications, Population, and The Contribution of Medical Health Libraries to Health Statistics.

The University of Minnesota announces a Symposium on Metabolism of Potassium (sponsored by the M & R Laboratories, Inc., Columbus, Ohio). The symposium will be held in Minneapolis on September 22, 23 and 24, 1952. Experimental and clinical aspects of potassium metabolism will be presented by outstanding investigators from various medical centers. The detailed program will be announced at a later date. For further information, write to the Director of Continuation Medical Education, University of Minnesota Hospital, Minneapolis-14, Minnesota.

The American Trudeau Society, Medical Section of the National Tuberculosis Association, invites the submission of abstracts of scientific papers for presentation at its next annual meeting in Los Angeles, California, May 18 to 22, 1953, at the Hotel Statler.

Full information can be obtained by writing to the Chairman of the Medical Sessions Committee, American Trudeau Society, 1790 Broadway, New York 19, N. Y.

The sessions of the Sixth Connecticut Postgraduate Seminar in Psychiatry and Neurology will begin on October 1, 1952, and will continue through May 4, 1953.

From October 1 through December 12, 1952, sessions in clinical neurology, neuroroentgenology, electroencephalography, neuroanatomy, neurophysiology, neuropathology, and review and demonstrations in neuroanatomy and neuropathology will be held on Mondays and Wednesdays from 4:00 p.m. to 9:30 p.m. at Yale University School of Medicine, New Haven.

On Mondays, from January 5 through March 2, 1953, 4:00 to 9:30 p.m., courses in clinical psychology, general psychopathology, psychiatric syndromes, therapy, psychosomatic medicine, geriatric psychiatry, and psychiatry and law will be held at the Connecticut State Hospital.

From March 9 through March 30, 1953 (Mondays), from 4:00 to 9:30 p.m., a course in child psychiatry will be held at the Child Study Center of Yale University, New Haven; and a course in pediatric neurology will be held from April 6 through May 4, 1953, at Yale University School of Medicine, New Haven, from 6:45 to 9:45 p.m.

There are no fees for the above courses. Copies of the program may be obtained from the Office of the Assistant Dean for Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut.

West Virginia Holds First Regional Meeting

The West Virginia members of the American College of Physicians held their first Regional Meeting, during the meeting of the West Virginia State Medical Association, at White Sulphur Springs, Friday, July 25, 1952, under the Governorship of Dr. Paul H. Revercomb, F.A.C.P. Speakers on the Program included Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., "Space Medicine"; Dr. Charles M. Caravati, F.A.C.P., Richmond, Va., A.C.P. Governor for Virginia, "Jaundice, Its Clinical Interpretation"; and Dr. Alphonse McMahon, F.A.C.P., St. Louis, Mo., "Hypercholesterolemia." Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa., President of the College, was an official guest and delivered the banquet address in the evening.

Dr. Miller and Dr. McMahon were also guest speakers on the program of the West Virginia State Medical Association.

Coming A. C. P. Regional Meetings

Western New York at Syracuse, October 3.
Montana and Wyoming at Great Falls, Mont., October 10–11.
Western Pennsylvania at Pittsburgh, October 11.
Pacific Northwest at Vancouver, B. C., October 17–18.
Arizona and New Mexico at Albuquerque, October 29.
New Jersey at Newark, November 5.
Southeastern at Havana, Cuba, November 7–8–9.
Midwest at Chicago, November 22.
North Carolina at Winston-Salem, December 4.
Eastern Pennsylvania at Philadelphia, January 16, 1953.
Colorado at Denver, February 17.
Virginia, February 26.
Kansas at Kansas City, March 20.

Dr. White Receives A. M. A. Distinguished Service Award

Dr. Paul Dudley White, F.A.C.P., Boston, Mass., became the recipient of the Distinguished Service Medal of the American Medical Association for 1952 at the annual meeting of the Association in Chicago in June. One of the nation's outstanding cardiologists, Dr. White is Executive Director of the National Advisory Heart Council and is Chief Consultant to the National Heart Institute. In addition to his fellowships in the College and the A. M. A., Dr. White also holds memberships in the Royal Society of Medicine, London; the American Heart Association; the Association of American Physicians, and the American Society for Clinical Investigation.

At the same meeting, Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., assumed the presidency of the Association, succeeding Dr. John W. Cline, San Francisco.

Dr. Francis F. Borzell, F.A.C.P., Philadelphia, retired as Speaker of the House of Delegates, and was succeeded by Dr. James R. Reuling, Jr., F.A.C.P., Bayside, N. Y.

Students Honor Teachers

Dr. Gerald Klatskin, F.A.C.P., Associate Professor of Medicine at the Yale University School of Medicine, has received the first Francis Gilman Blake Award of the Yale chapter of Nu Sigma Nu. The award, which will be given annually and is determined by a vote of the graduating class, was established "to encourage better teaching of the medical sciences by recalling the example set by Dr. Blake." Dr. Blake, late Dean of the School of Medicine, was also a Fellow of the College.

Students at the University of Illinois College of Medicine also honored five faculty members. Dr. Murray Franklin (Associate) was one of those who received gold keys, emblematic of the annual Raymond B. Allen instructorship awards, designed to honor excellency in instructorship rendered by the faculty members to students. Dr. Franklin is Assistant Professor of Internal Medicine at the University.

Dr. Roger M. Choisser, F.A.C.P., Professor of Pathology at the George Washington University School of Medicine, received the University Medical Society's Annual Award of Merit at a meeting of the Society held late in the spring. Dr. Choisser has been a member of the University faculty for more than thirty years.

Dr. Harrold A. Murray, F.A.C.P., Newark, N. J., received the honorary degree of LL.D. from Seton Hall University, June 8.

Dr. J. Burns Amberson, F.A.C.P., New York, recently received the annual Trudeau Medal, awarded by the National Tuberculosis Association, for "the most meritorious contribution on the cause, prevention or treatment of tuberculosis."

Dr. Mary Elizabeth Bass, F.A.C.P., Lumberton, Miss., received the Alumnae Achievement Award from the Woman's Medical College of Pennsylvania in Philadelphia on June 9. Professor Emeritus of Medicine at Tulane University of Louisiana School of Medicine, Dr. Bass retired in 1941 after thirty years of service at Tulane.

Dr. Francis D. Murphy, F.A.C.P., Director of the Department of Medicine at Marquette University School of Medicine, received the annual medical alumni award from Marquette University on March 29.

Dr. Nathan B. Van Etten, F.A.C.P., New York, was one of two to receive meritorious awards from the alumni of New York University College of Medicine at their annual dinner on May 20. Dr. Van Etten has also been honored by the naming of the Nathan B. Van Etten Hospital, which will accommodate 500 tubercular patients and which is now under construction in the Bronx.

Dr. Joseph T. Roberts, F.A.C.P., of the Veterans Administration Hospital, Buffalo, N. Y., was awarded a Certificate of Merit for the best scientific exhibit of the Section of Internal Medicine at the annual meeting of the American Medical Association at Chicago in June.

Dr. Eugene A. Stead, Jr., F.A.C.P., Durham, N. C., was elected President of the American Society for Clinical Investigation at the annual meeting of the Society in Atlantic City, May 5. At the same meeting, Dr. Carl V. Moore, F.A.C.P., St. Louis, was made Vice-President.

Dr. Robert G. McCorkle, Sr., F.A.C.P., San Antonio, Tex., was elected to the presidency of the American Academy of Tuberculosis Physicians at their annual meeting in Chicago, June 7.

Meeting in Hollywood, Fla., April 29–30, the Florida Medical Association named Dr. Frederick K. Herpel, F.A.C.P., West Palm Beach, President-Elect.

The American Psychiatric Association, meeting in Atlantic City, May 12–16, chose Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, as President-Elect, and elected Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va., Secretary for the third successive year.

Dr. George M. Lewis, F.A.C.P., New York, was reëlected Secretary-Treasurer of the American Board of Dermatology at its annual meeting in Chicago, May 8.

Dr. George N. Thompson, F.A.C.P., Los Angeles, was elected Secretary-Treasurer of the Society of Biological Psychiatry when the Society held its annual convention in Atlantic City on May 11.

Dr. William P. Harbin, Jr., F.A.C.P., Rome, became President-Elect of the Medical Association of Georgia at the Association's annual meeting in Atlanta, May 11–14.

Dr. Orval R. Withers, F.A.C.P., Kansas City, Mo., was elected President of the Southwest Allergy Forum at its meeting in Dallas, Tex., late in the spring.

Dr. Lowell T. Coggeshall, F.A.C.P., Dean of the University of Chicago Division of Biological Sciences, has recently been elected President of the Chicago Society of Internal Medicine.

Dr. Mark Lewis Gerstle, Jr., F.A.C.P., addressed the New York Academy of Medicine on April 22. The title of his paper was "The Liaison Psychiatrist—His Rôle in Gynecology."

In addition to Dr. Irving S. Wright, F.A.C.P., New York, A.C.P. Governor for Eastern New York, who was installed as President of the American Heart Association at its annual meeting in Cleveland in April, Dr. Robert L. King, F.A.C.P., Seattle, Wash., was chosen President-Elect. Among the vice-presidents elected were: Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn.; Dr. E. Cowles Andrus, F.A.C.P., Baltimore; Dr. Irvine H. Page, F.A.C.P., Cleveland; and Dr. John J. Sampson, F.A.C.P., San Francisco.

Dr. Norman Jolliffe, F.A.C.P., Director of the Bureau of Nutrition of the New York City Department of Health, was elected President of the National Vitamin Foundation, Inc., at its annual meeting in New York on April 3.

At the annual session of the Maine Medical Association, held in Rockland, June 22–24, Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., delivered the banquet address. Dr. William B. Terhune, F.A.C.P., New Canaan, Conn., was one of the out-of-state speakers, his topic being "Making the Most of Man."

Guest speakers at the annual Rocky Mountain Cancer Conference, held in Denver, July 9–10, included Dr. George R. Meneely, F.A.C.P., Nashville, Tenn.; Dr. Cornelius P. Rhoads, F.A.C.P., New York; and Dr. Edward P. Cawley (Associate), Charlottesville, Va.

Among the delegates to the Fourth Inter-Cardiological Congress, representing the American Heart Association, are Dr. Irving S. Wright, F.A.C.P., New York; Dr. Louis N. Katz, F.A.C.P., Chicago; Dr. Howard B. Sprague, F.A.C.P., Brookline, Mass.; Dr. Lewis Dexter, F.A.C.P., Boston; Dr. George R. Herrman, III, F.A.C.P., Galveston, Tex.; and Dr. Carl J. Wiggers, F.A.C.P., Cleveland. Under the auspices of the Argentine Society of Cardiology, the Congress will be held in Buenos Aires, Sept. 1–6.

Under the presidency of Dr. Samuel A. Levinson, F.A.C.P., Chicago, the fourth annual meeting of the American Academy of Forensic Sciences was held in Atlanta, Ga., March 6–8. Dr. William E. B. Hall, F.A.C.P., Chambersburg, Pa., was among the speakers.

Dr. Elliott P. Joslin, M.A.C.P., Boston, Honorary President of the American Diabetes Association, presented the Award to the Banting Memorial Lecturer at the Association's twelfth annual meeting in Chicago, June 7–8. Dr. Arthur R. Colwell, Sr., F.A.C.P., Chicago, President of the Association, also addressed the guests at the dinner at which the presentation was made.

Among those taking part in the scientific sections of the meeting, which included a joint session with the Endocrine Society, were: Dr. Alexander Marble, F.A.C.P., and Dr. George W. Thorn, F.A.C.P., Boston; Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif.; Dr. David Adlersberg, F.A.C.P., New York; Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia; Dr. Cecil Striker, F.A.C.P., Cincinnati; Dr. Joseph H. Crampton, F.A.C.P., Seattle; Dr. T. S. Danowski, F.A.C.P., Pittsburgh; Dr. Howard F. Root, F.A.C.P., Boston; and Dr. Edward S. Dillon, F.A.C.P., Dr. Russell Richardson, F.A.C.P., and Dr. David A. Cooper, F.A.C.P., all of Philadelphia.

Dr. Jerome W. Conn, F.A.C.P., Ann Arbor; Dr. Samuel Soskin, F.A.C.P., and Dr. Henry T. Ricketts, F.A.C.P., Chicago; Dr. Robert W. Schneider, F.A.C.P., Cleveland; Dr. William R. Jordan, F.A.C.P., Richmond, Va.; and Dr. Herbert Pollack, F.A.C.P., New York, were among those who participated in the panel discussions.

Dr. J. Edward Berk, F.A.C.P., Philadelphia; Dr. John R. Haserick (Associate), Cleveland; and Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn., were among the guest speakers at the annual meeting of the Oklahoma Medical Association, held May 19–21 in Oklahoma City. Among the Association members who participated in the scientific sessions were Dr. R. Q. Goodwin, F.A.C.P., Dr. Moorman P. Prosser, F.A.C.P., Dr. Edward C. Reifenstein, Jr., F.A.C.P., and Dr. James R. Colvert (Associate), Oklahoma City. Among those who presented papers by title were Dr. Joseph I. Goodman, F.A.C.P., and Dr. Edward Schwartz, F.A.C.P., Cleveland Heights; Dr. Barnett Greenhouse, F.A.C.P., New Haven; Dr. Henry J. John, F.A.C.P., Cleveland; and Dr. Maxwell Spring (Associate), Bronx, N. Y.

Dr. J. Shirley Sweeney, F.A.C.P., Gainesville, Tex., delivered the Frank Vinsonhaver Memorial Lecture at the University of Arkansas School of Medicine, Little Rock, May 30. His topic was "Changes in Medical Practice."

Dr. Harold D. Levine, F.A.C.P., Clinical Associate in Medicine at Harvard Medical School and Associate in Medicine at Peter Bent Brigham Hospital, Boston, delivered the Annual Phi Chi Lecture at the Medical College of Virginia, Richmond, on May 9. His subject was "The Non-specificity of the Electrocardiogram Associated with Coronary Artery Disease."

Dr. J. A. E. Eyster, F.A.C.P., Madison, Wis., has recently retired as Chairman of the Department of Physiology of the University of Wisconsin Medical School. He plans, however, to continue his research into electric characteristics of injuries to heart muscle, doing much of his work in the University laboratory. Dr. Eyster was associated with the Department for 41 years.

Dr. C. Robert Newman (Associate) on July 1 removed from Redwood City, Calif., to Racine, Wis., where he will continue the practice of internal medicine as a specialty.

Dr. I. S. Freiman, F.A.C.P., New York, has been promoted to Associate Neurologist at the Mount Sinai Hospital and to Associate Clinical Professor of Neurology at New York University College of Medicine.

OBITUARIES

DR. HARVEY GRANT BECK

The death of Dr. Harvey Grant Beck, F.A.C.P., of Baltimore removes a loyal and devoted member from the rolls of the American College of Physicians. He was eighty-one years of age at the time of his death, October 30, 1951. Despite his years, his interest in medical practice never waned. His association with the College dated from Fellow in 1920; he was always an enthusiastic member; he was a regular attendant at its meetings, both regional and annual; and he was a former College Governor for Maryland (1929–31).

Dr. Beck's beginnings were modest ones. Born in York, Pa., August 15, 1870, he went to Baltimore when he neared his majority with the intent of studying pharmacy. In 1893, when he graduated from the Maryland College of Pharmacy at the head of his class, his honor work had attracted the attention of his teachers, and he was advised to study medicine. Dr. Beck again distinguished himself by leading his medical class, receiving his M.D. degree in 1896 at the College of Physicians and Surgeons, Baltimore. Postgraduate study followed at the University of Vienna, the Johns Hopkins University School of Medicine, and the University of Berlin. His subsequent career combined medical practice with medical teaching. Dr. Beck almost at the beginning limited his practice to internal medicine, a pioneer venture in the early 1900's, and he displayed especial interest in endocrinology. His success and his reputation led to the founding of the Beck Clinic in 1926. For many years he was on the staff of Union Memorial, Sinai, Franklin Square, and South Baltimore General hospitals, and the Church Home and Hospital. From 1910 to 1914 he was Professor of Clinical Medicine at the College of Physicians and Surgeons, and from 1914 to 1946 he was Professor of Clinical Medicine at the University of Maryland School of Medicine, whence he became Professor Emeritus. As a teacher, Dr. Beck was devoted to his students, and he exerted a profound influence on the younger men privileged to study under him.

He was a member of numerous professional societies; he was one-time President of the Baltimore City Medical Society, American Therapeutic Society, Biological Society of University of Maryland; and former Vice-President of the Medical and Chirurgical Faculty of Maryland. For years Dr. Beck was an investigator in carbon monoxide poisoning. At one time he was director of a clinical survey of a combustion product study sponsored by the Resources Committee, West Virginia University.

Dr. Harvey Beck was widely known beyond the medical sphere of Baltimore. Everywhere he was regarded with esteem.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P.,
Governor for Maryland

DR. JAMES LEWIS BIBB

James Lewis Bibb, A.B., M.D., F.A.C.P., Chief of Staff of Baroness Erlanger Hospital, Chattanooga, Tenn., died on February 17, 1952, of coronary thrombosis at Memorial Hospital, Chattanooga. He was 66 years of age. He had been in ill health for several years but continued with his professional and civic activities until the day before his death.

Dr. Bibb was born in Charlottesville, Va., on May 21, 1885. He attended the University of Virginia, from which he received a Bachelor of Arts degree in 1908 and a Doctor of Medicine degree in 1912. After graduation, his hospital training included services in Martha Jefferson Hospital and University of Virginia Hospital, Charlottesville, and in Bellevue Hospital, New York City. He began the practice of Internal Medicine in Chattanooga in 1913.

In addition to his active practice, he was very generous in his contributions of time and energy to the medical societies of which he was a member. He was a past president of the Chattanooga-Hamilton County Medical Society and a past vice-president of the Tennessee State Medical Society. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1925.

Dr. Bibb's ideals were high. He strove untiringly to elevate the standards of the profession and to advance the means for preventing and treating disease in the city where he labored for forty years. To quote from an editorial in one of the Chattanooga papers, "Dr. Bibb lived as unselfishly as he died. Besides attending his practice, he found time to serve as a leader in his profession, to advance the cause of preventive medicine and to improve the facilities for medical treatment in the community."

CONLEY H. SANFORD, M.D., F.A.C.P.,
Governor for Tennessee

DR. RUSSELL LANDRAM HADEN

It is said that men develop qualities of strength and stamina, of insight and tolerance, and of the insatiable curiosity of the investigator by reason of their close communion with nature and their love of the soil. If this be so, we may have part of the secret behind the strong body and valiant spirit of Russell Landram Haden (A.B., M.A., M.D., F.A.C.P.). Dr. Haden's earlier and later life on a Virginia farm cultivated in him an "at-homeness" with nature which extended to all kinds of people. His interest in growing things, whether utilitarian or beautiful, remained always in the forefront of his thinking and conversation; and farm animals and orchardry continued to be of concern to him throughout his life. A beautiful garden was an essential part of his living. Farm community life cultivated in him the quality of enjoying and understanding peoples so that he possessed to a rare degree the ability to make others comfortable and at ease, no matter what the occasion.

In what appeared to be the full maturity of a rich life, Dr. Haden came to the Cleveland meetings of the American College of Physicians for the week of April 21, 1952, to renew old friendships in the city where he had been Chief of the Medical Division of the Cleveland Clinic for 18 years, and to greet the multitude of personal friends among the physicians throughout the length and breadth of this land who had gathered there. He was enthusiastic about the progress being made in the more effective preservation of the formed elements of the blood in his capacity as Medical Director of the National Blood Program of the American Red Cross. He was eager, as always, to accumulate and disseminate new knowledge about the red blood cells.

On Thursday morning, April 24, with all of the animation and assurance which his first-hand experience and knowledge made a very natural part of his powers of clear presentation, he joined his former colleagues at the Cleveland Clinic in the presentation of a color-televised clinic on hemolytic anemia. However, just at the conclusion of this characteristically dynamic clinic, the development of a sudden headache heralded the vascular accident from which he was unable to recover. His death occurred at 3:00 a.m. on Saturday, April 26, 1952, in the Clinic, where he was surrounded and attended by the friends with whom he had studied and practiced medicine until the time of his retirement from active clinical medicine in 1948.

Dr. Haden was born in Palmyra, Virginia, on May 22, 1888. He received his Bachelor's and Master's degrees in Arts from the University of Virginia in 1910 and 1911, respectively. He then went to Johns Hopkins University School of Medicine, receiving his M.D. degree in 1915. He remained at the Johns Hopkins Hospital as Medical House Officer during 1915–16, and was Assistant Resident from 1916 to 1918. He then went as Chief of Laboratories to the Henry Ford Hospital in Detroit, re-

maining there between the years 1918 and 1921. He was Assistant Chief of the Medical Service at the Base Hospital, Camp Lee, Virginia, during 1918–19. In 1921 he went to the University of Kansas School of Medicine as Associate Professor in the Department of Medicine and Professor of Experimental Medicine, which positions he held until 1930.

Dr. Haden then went to the Cleveland Clinic as Chief of the Medical Division, which position he held until his official retirement in 1948. He had long anticipated retirement to Crozet, Virginia, where he had been preparing a lovely home retreat on a farm and in a county which had been owned and dominated by the Haden family for several generations. It was his great pleasure and delight to bring his many medical friends to this beautiful spot in the Blue Ridge Mountains and to expatiate on the joys and satisfactions of retirement.

But Dr. Haden had "retired" from only the Cleveland, Kansas City, Detroit and Baltimore scenes of his previous medical activities. He immediately became Active Consultant in Hematology to the Surgeons General of the U. S. Army and U. S. Navy in nearby Washington, D. C., making regular ward rounds at the various medical centers in the District of Columbia. The Committee on Policies and Procedures of the National American Red Cross, in seeking a Medical Director for the National Blood Program, found in Russell Haden a "natural" for this fulfillment of a national need in the field of his lifelong interest, the red blood cell. It was not difficult to persuade him to accept the directorship of this program, both because of a natural interest and because of the great national need. It was with all of the enthusiasm and vigor of youth that he assumed the leadership in this program, making trips throughout this country and abroad, to both Europe and the Far East, in the interest of this program and in the interest of the better medical care of our Armed Forces, wherever they have been sent.

He repeatedly said, "Doing what you want to do is the epitome of life, and I am doing what I want to do."

Dr. Haden took great pride in his sons and their achievements and in the understanding and loving wife who complemented his every desire and wish.

He died as he would have wished it—with week ends in retirement at Crozet, but in the high noon of mid-day, mid-week, always with his medical friends, planning for further advancements in the great field of medicine.

Dr. Haden had assumed leadership in all of the many medical organizations with which he inevitably became associated. He was a valued councillor of the American Medical Association. He was President of the Academy of Medicine in Kansas City and, later, of the Academy of Medicine of Cleveland during his periods of residence in each of these cities. He was President of the American Society for the Study and Control of Rheumatic Diseases. He was an active member of the American Society for Clinical Investigation, the Central Society for Clinical Research, the American Clinical and Climatological Association, the Association of American Physicians, the American Society of Clinical Pathologists, and the American Associations of Pathology and Bacteriology. He had been a Fellow of the American College of Physicians since 1937. A Diplomate of the American Board of Internal Medicine, he was the author of more than 200 publications dealing with the various aspects of internal medicine to which he gave thought and attention. Particularly was he appreciative of the contributions of those of earlier generations who had laid the foundation for modern medical progress.

Few men of his generation have been given to enjoy so many warm personal friends, among both fellow-physicians and patients, and few have been privileged to live so fully and satisfyingly and to accomplish so much coöperatively with their contemporaries.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

THE AMERICAN COLLEGE OF PHYSICIANS
ABSTRACT OF MINUTES, BOARD OF REGENTS
CLEVELAND, OHIO, APRIL 22, 1952

The second meeting of the Board of Regents, during the Thirty-third Annual Session, convened April 22, 1952, at the Cleveland Public Auditorium, Cleveland, Ohio, with President Maurice C. Pincoffs presiding, Mr. E. R. Loveland acting as Secretary and with twenty-one Regents in attendance. Abstracts of the Minutes of the previous meeting of the Board were read by the Secretary and approved.

Dr. Edward L. Bortz, Chairman of the Committee on Constitution and By-Laws, in accordance with directions given by the Board of Regents, presented an amendment to the By-Laws, Article VII, Section 4, providing that the maximal Associate term be extended from five years to ten years. The amendment was unanimously approved and the Secretary-General directed to present it at the Annual Business Meeting to follow on April 24, 1952.

Dr. Walter L. Palmer, as Chairman of a special committee for the purpose, presented an Interpretation of the amendment to the By-Laws, which, by resolution, was adopted. This Interpretation is not repeated herein, because it appears in the Minutes of the Annual Business Meeting.

The Secretary recorded that by appointment by President Maurice C. Pincoffs, Dr. Lemuel C. McGee had accepted an appointment as representative of the American College of Physicians on the Advisory Board of the American Federation of Occupational Health.

The Secretary presented a letter from the World Medical Association, soliciting a contribution in 1952 for the support of that Association. A motion was adopted that while the College has full sympathy with the objectives of the World Medical Association and while it made a contribution in its earlier state of development, at the present time it was the consensus of the Board that further contributions are somewhat outside of the real objectives of the College, and by resolution a further contribution at this time was not approved.

Dr. Cyrus C. Sturgis, Chairman of the Committee on Fellowships and Awards, presented the following report: "The Committee on Fellowships and Awards met at the Public Auditorium, Cleveland, Ohio, 10:00 A.M., April 20, 1952, with the Chairman, Cyrus C. Sturgis, presiding and with Dr. Herbert K. Detweiler, Dr. T. Grier Miller, Dr. Walter L. Palmer of the Committee in attendance, and with Dr. M. R. Kinde, of the Kellogg Foundation, and Dr. E. Hugh Luckey, Director of the Orientation Course, as guests. Dr. Wesley W. Spink was absent.

"The first order of business considered was means of continuing the Orientation Course at Bellevue Hospital, New York City, for Latin-American Fellows. This course, supervised by Dr. E. Hugh Luckey, has been an important part of the training of these fellows, but Cornell University has recently stated that it could not continue the course for financial reasons. This matter was discussed fully with Dr. M. R. Kinde, of the Kellogg Foundation, and he states that the Kellogg Foundation will pay a tuition of $1,000.00 per student instead of the former $500.00. This will insure continuation of the course.

"The records of ten Latin-American Fellows appointed in 1950 were reviewed, and arrangements made to forward certificates to them, signed by appropriate Preceptors. These were as follows:

Dr. Guido BATTILANA, Daso, Lima, Peru
(Preceptors, Dr. Eugene C. Eppinger and Dr. C. Sidney Burwell)
Dr. Fructuoso BIEL Cascante, Concepcion, Chile

(Certificate issued; Preceptor, Dr. Thomas E. Machella)
Dr. Aloysio de Salles FONSECA, Rio de Janeiro, Brazil
(Preceptor, Dr. Cyrus C. Sturgis)
Dr. Egon LICHTENBERGER Salomon, Bogota, Colombia
(Certificate issued; Preceptor, Dr. Paul Klemperer)
Dr. Jorge MAISTERRENA Fernandez, Mexico, D. F.
(Preceptors, Dr. George W. Thorn and Dr. John B. Stanbury)
Dr. Hector ORREGO Matte, Santiago, Chile
(Preceptors, Dr. Henry L. Bockus and Dr. Cecil J. Watson)
Dr. Ruy PEREZ TAMAYO, Mexico, D. F.
(Preceptor, Dr. Robert A. Moore)
Dr. Valdir Cordeiro PESSOA, Recife, Brazil
(Preceptor, Dr. A. C. Ivy)
Dr. Silvio Humberto RODAS Ortiz, Asuncion, Paraguay
(Preceptor, Dr. Franklin D. Johnston)
Dr. Roberto Figueira SANTOS, Salvador, Brazil
(Preceptor, Dr. Cyrus C. Sturgis)

"Likewise, the records of the 1951 Latin-American Fellows were reviewed, and reports on each one, as written by Dr. E. Hugh Luckey, were considered. These men, and their Preceptors, are as follows:

Dr. Jorge ARAUJO Grau, Bogota, Colombia, under Preceptorship, Dr. E. Hugh Luckey and Dr. David P. Barr, New York Hospital.

Dr. Jose BARZELATTO Sanchez, Santiago, Chile, under Preceptorship, Dr. Walter Bauer, Massachusetts General Hospital.

Dr. Adolfo BISSO Zollner, Lima, Peru, under Preceptorship, Dr. Francis C. Wood, University of Pennsylvania School of Medicine.

Dr. Jose CARA, Cordoba, Argentina, under Preceptorship, Dr. Lawson Wilkins, Johns Hopkins Hospital.

Dr. Alvaro CARBALLO Montero, San Jose, Costa Rica, under Preceptorship, Dr. H. Marvin Pollard, University of Michigan Hospital.

Dr. Jose Antonio GARCIA Reyes, Mexico, D. F., under Preceptorship, Dr. George W. Thorn, Peter Bent Brigham Hospital, then under Preceptorship, Dr. Peter H. Forsham, University of California.

Dr. Carlos HEINRICH Treuer, Concepcion, Chile, under Preceptorship, Dr. Gordon B. Myers, Wayne University School of Medicine.

Dr. Otto HERRMAN Koch, Santiago, Chile, under Preceptorship, Dr. Irving S. Wright, New York Hospital.

Dr. Arturo PINEDA Giraldo, Medellin, Colombia, under Preceptorship, Dr. Walter L. Palmer, University of Chicago.

Dr. Francisco RIVADENEYRA Hinojosa, Morelia, Mexico, under Preceptorship, Dr. Sara M. Jordan, Lahey Clinic, Boston.

"Dr. Jose M. PORTILLA, Quito, Ecuador, has been awarded a fellowship, but has been unable to report due to unavailability of local funds.

"At an earlier time the Committee on Fellowships and Awards had decided that the Executive Office should issue certificates, signed by the proper authorities, to each Latin-American Fellow before he left for his return to his home country. Experience has shown that this is often impractical, in view of the fact that there are unavoidable delays in getting the signatures of preceptors or of officers of the College, and often impossible to determine the exact date when the Fellows complete

their work. In such cases, the Executive Office has been authorized to complete the certificate and to deliver it to the Fellow by mail.

"The records of the six current Research Fellows of the College were reviewed, as follows:

(1) Dr. John William Athens
$3,500.00; to work at Johns Hopkins Hospital, under Dr. F. W. Barnes, Jr., Preceptor; field, protein regeneration.

(2) Dr. Sidney Harold Ingbar
$3,500.00; to work at Thorndike Memorial Laboratory, under Dr. Maxwell Finland, Preceptor; field, metabolic physiology of infection.

(3) Dr. James Edwin Wood, III
$3,500.00; to work at Evans Memorial, Massachusetts Memorial Hospitals under Dr. Robert W. Wilkins, Preceptor; field, circulation in the extremities.

"The above three Research Fellows are on military service, and their fellowship stipends are being held, pending their release from active duty.

(4) Dr. Amoz Immanuel Chernoff
$3,000.00; Department of Hematology, Washington University School of Medicine, under Dr. Carl V. Moore, Preceptor; field, hemolytic anemias.

(5) Dr. John William Harris (Alfred Stengel Research Fellow)
$3,500.00; Thorndike Memorial Laboratory, Boston City Hospital, under Dr. William B. Castle; field, hematology.

(6) Dr. John Edmund Kiley
$3,500.00; Albany Medical College, under Dr. A. V. Wolf and Dr. William B. Deichmann, Preceptors; field, renal diseases.

"The four Research Fellowships awarded for the period July 1, 1952, through June 30, 1953, to the following, have been accepted to start as designated:

(1) Dr. Calvin Ezrin (Alfred Stengel Research Fellow)
$4,000.00; University of Toronto School of Medicine, Dr. Ray F. Farquharson, Preceptor; field, effect of severe malnutrition from various causes on endocrine structure and function; accepted to start July 1, 1952.

(2) Dr. Thomas William Fyles
$3,000.00; McGill University Clinic, Royal Victoria Hospital, Dr. Bram Rose, Preceptor; field, effect of ACTH and Cortisone on asthma; accepted to start July 1, 1952.

(3) Dr. Ladd Watts Hamrick, Jr.
$3,000.00; Duke Hospital, Dr. J. D. Myers, Preceptor; field, splanchnic blood flow and metabolism; accepted to start July 1, 1952.

(4) Dr. Avard Marion Mitchell
$3,000.00; Peter Bent Brigham Hospital, Dr. Samuel A. Levine, Preceptor; field, cardiovascular diseases; accepted to start July 1, 1952.

"A final report was given by Dr. Benjamin B. Wells, the first recipient of the A. Blaine Brower Traveling Scholarship for 1951, saying he had completed his travels.

"Dr. Daniel Harvey Labby, of the University of Oregon, Portland, Ore., one of the recipients for the 1952, A. Blaine Brower Traveling Scholarships, submitted a comprehensive report concerning his traveling scholarship, which has now been concluded.

"Dr. William H. Bates, Cottonwood, Ariz., the other recipient of the 1952 A. Blaine Brower Traveling Scholarships, is to confer with the Chairman of the Committee to arrange for a period of one month during the summer of 1952 in Boston.

"There was some discussion concerning the stipends of the Research Fellowships of the College, and consideration was given to a list of fellowships in this country and the amounts paid by each organization. It was the consensus of the Committee that our fellowship stipends should probably be increased, but that final action should not be taken in regard to this until at the June or November meeting of the Committee.

"It was decided to hold the next meeting of the Committee in June, 1952, in Ann Arbor, Mich., to consider a group of fifteen new Latin-American Fellows, who have been recommended by the Kellogg Foundation.

"Also, at this time, the Committee asks authorization to select the nominees for the John Phillips Memorial Award and the James D. Bruce Memorial Award, subject to the approval of the Executive Committee, at the June, 1952, meeting, as in the past year."

By formal resolution, the report was accepted and the recommendations of the Committee approved. Furthermore, a special resolution of thanks, on behalf of the Board of Regents to the Committee on Fellowships and Awards, was adopted.

Dr. A. B. Brower, Chairman of the Committee on Finance, presented the annual report, in part as follows:

"Mr. President and Members of the Board, the Committee on Finance met at the Public Auditorium on April 20, 1952, with Doctors A. B. Brower, Chairman, Walter B. Martin, Walter L. Palmer, the Treasurer and the Executive Secretary in attendance.

I. Auditor's Report for 1951:

(1) Salient Data:
(a) All accounts audited by a Certified Public Accountant.
(b) Increase in Funds:

	Balance Jan. 1, 1951	*Balance Dec. 31, 1951*	*Increase*
Endowment Fund	$333,833.42	$347,079.60	$ 13,246.18
James D. Bruce Fund	10,000.00	10,000.00	
A. Blaine Brower Fund	10,000.00	20,000.00	10,000.00
General Fund	412,298.25	508,144.00	95,845.75
Restricted Funds	770.83	1,496.32	725.49
	$766,902.50	$886,719.92	$119,817.42

(c) Gross Assets of the College—$886,719.92.
(d) Endowment Fund Data:
Life Membership Fees, 1951, $16,385.00 (1950, $17,561.67; 1949, $16,540.00).
Profit on Endowment Fund Security Transactions, $2,966.18.
(e) General Fund Data:

	1950	*1951*
Total Income	$298,982.55	$338,270.18
Total Expenses	205,649.61	222,484.43
	$ 93,332.94	$115,785.75

(f) General Comments and Comparisons:

	1949	*1950*	*1951*
Annual Dues	$ 42,934.00	$ 44,838.85	$ 51,495.44
Initiation Fees	19,736.00	23,065.00	20,875.00
Annals, Subscriptions	99,502.77	125,629.57	127,304.08
Annals, Advertising	23,148.26	31,809.07	58,936.88
Annals, Expenses	83,347.83	98,851.60	120,867.60
Annual Session, Net Cost	5,088.11	464.89	5,655.84*
Total Income, General Fund	236,649.40	298,982.55	338,270.18
Total Expenses, General Fund	174,514.11	205,649.61	222,484.43
Net Income, General Fund	62,135.29	93,332.94	115,785.75

* Net Profit.

(g) The Auditor's Report and Detailed Financial Statements disclose all details and give a certified registry of all investments.

"The Committee recommends a change in the percentage of common stocks and bonds, and we have asked Drexel & Co. to recommend the sale of certain common stocks and the purchase of certain bonds, so that there will be a change in the percentage of about 10%. It is the desire of the Committee for the Board of Regents to know that this will make a reduction in our income of about .35%.

"The current distribution of securities, Endowment and General Funds combined, is as follows:

Bonds	30.5%	U. S. Government	17.2%
Preferred Stocks	13.6%	Railroad	12.5%
Common Stocks	51.6%	Public Utility	21.8%
	95.7%	Industrial	35.1%
Uninvested Cash	4.3%	Bank	9.1%
	100.0%	Uninvested Cash	4.3%
			100.0%

Average Yield, 4.35% (1949, 4.28%; 1950, 4.66%).

"Comparison of Cost and Current Value of our Investments (all Funds):

Cost or Book Value	*Current Market Value**	*Appreciation*
$720,610.96	$836,661.00	$116,050.04"

* 3-28-52.

Dr. Brower also reported in detail on all security transactions executed since the last meeting of the Board of Regents, presented a recommendation that excess cash that might be needed late in the year might now be invested in short term securities, and presented a list of items to be added to the 1952 budget.

By resolution formally adopted, the entire report was approved and each recommendation authorized.

Dr. LeRoy H. Sloan, Chairman of the Committee on Public Relations, presented a report for that Committee. Arising out of communications that had been reviewed by the Committee, the following actions were taken:

(1) Regarding the admission of Doctors of Osteopathy to the Annual Sessions of the College, it was pointed out that they are not members of the American Medical Association and cannot be granted the courtesies of our Annual Sessions, for the Board of Regents has not provided any alternative for the admission of non-members;

(2) Regarding an inquiry concerning the admission of Doctors of Osteopathy to practice Internal Medicine and Surgery in a municipal general hospital, the problem was considered one for local solution and for submission to the American Medical Association for handling on that level;

(3) Regarding the admission for personal hearing before the Board of Regents of an official representative of the National Doctors Committee for Improved Federal Medical Services, it was the consensus that this is a matter about which the Board of Regents does not care to take action at this time;

(4) Regarding medical and hospital benefits for veterans with non-service connected disabilities, benefits for dependents of service personnel and transfer of seriously disabled service personnel from service hospitals to Veterans Administration installations, a subject presented by the Secretary of the Committee on Legislation of the American Medical Association, it was considered this matter is most closely allied to the American Medical Association, but that the College would co-operate in any helpful way possible, as it may concern the field of Internal Medicine only;

(5) Regarding a communication from the American Academy of General Practice affecting hospital policies, no action was taken, because the matter probably will be handled in due time by the Joint Commission on Accreditation of Hospitals and through its new Director, Dr. Edwin L. Crosby.

On recommendation of this Committee, the election of an Associate was annulled, because he had not taken up his election within one year, but had expressed an absence of interest in the activities of the College; seven applications for waiver of dues, because of incapacitation and illness, were approved; the resignations of twenty-four Associates, largely due to their inability to qualify for Fellowship within the restricted period, and of two Fellows were accepted; one Fellow was dropped from the Roster because of delinquency in dues of more than two years' standing.

On recommendation of the Committee on Public Relations, a resolution was adopted by which the Regents authorized the study of group health and accident and/or professional liability insurance for its members, with authorization to the President to appoint a Committee on Insurance to study the matter and to report back at the next meeting of the Board during November, 1952.

Dr. Marion A. Blankenhorn, Chairman of the Committee on Educational Policy, presented a report at length, with the following recommendations:

"(1) That the Committee on Educational Policy be enlarged to five members, with yearly change in Chairman, and with continuity of members, and that this Committee be instructed to work in conjunction with the Advisory Committee on Postgraduate Courses, as at the present time;

"(2) That the Committee on Educational Policy be aided by two new subcommittees, to be appointed by the Regents and to be known as (a) Committee on Annual Scientific Programs and (b) Committee on Regional Meetings.

"The Committee on Educational Policy can then lead in studying the activities of the College and in advising the various Officers and Committees on matters of educational policy."

After general discussion, the proposal was tabled, in order that it may be brought up again at a time when there is more opportunity to have it given thought and careful discussion before the Regents.

Dr. Edward L. Bortz, Acting Chairman of the Advisory Committee on Postgraduate Courses, reported for that Committee, outlining in detail the schedule of proposed Postgraduate Courses to be offered by the College during the autumn of 1952 and the spring of 1953. A recommendation that the name of the Committee be changed to read "Committee on Postgraduate Courses" was approved. The Committee reported on one of the spring, 1952 courses, for which the Director suffered a material deficit, and recommended that the College reimburse the Director for the

deficit. The Committee expressed the opinion that Directors should properly budget their expenses and should not incur expenses in excess of the anticipated income, which they can readily determine from the minimum registration they have specified.

Dr. LeRoy H. Sloan, Chairman, presented the following report for the Conference Committee on Graduate Training in Medicine:

"The Committee recently met and approved a long list of hospitals that had made applications for residency programs. The Committee also turned down a group of hospitals that did not qualify. It made certain recommendations concerning the study of residencies in the State of Iowa, and received a good bit of information for the benefit of the Council on Medical Education and Hospitals from the balloon study, which was carried out in the State of Illinois. This balloon study was directed to about one hundred of the Fellows. Replies were returned by 5%, just enough to make approval concerning the residency programs in individual hospitals in the State of Illinois, and particularly in Chicago. There was a fair number who considered the program wonderful and recommended that it be carried on. There were many suggestions, particularly from heads of departments around Chicago, concerning the improvement of the residency program. The general feeling was that the residency program in Illinois should not be expanded, but should be improved, in institutions where it is now in force. Some hospitals were recommended for further investigation, because it was felt that their program were not being well administered. There is a Committee of the American Medical Association which is interested in studying internships. It has been sampling and surveying internships; its work will probably be brought to the attention of this Conference Committee. We feel the Conference Committee is effective and should be continued. It consists of two representatives from the American College of Physicians, two from the American Board of Internal Medicine and two from the American Medical Association."

Dr. Walter L. Palmer, Chairman of the American Board of Internal Medicine, reported on the activities of that Board. 1,588 candidates took the written examination in October, 1951; 818 passed—770 failed; percentage of failure 48.5%; the Board had held five oral examinations during 1951, the percentage of failures being 21.4% to 34%; approximately five oral examinations are planned for 1952.

Dr. Palmer further reported that the Board is in the process of revising the Articles of Incorporation, providing that it shall be a responsibility of the Chairman to make a report of the Board to the American College of Physicians and to the Section on Medicine of the American Medical Association. Further steps were being taken to establish a clear policy with respect to the interpretation of the Board's By-Laws with regard to partial terms and tenure of office of Board members. In the future a member of the Board elected to a partial term of one or two years will still be eligible for re-election for two terms of three years each.

Through Dr. Palmer, the Board presented a panel of nominees from which the Regents of the College shall elect new members on the Board, filling such vacancies as occur among the College's representatives on July 1, 1952. The Board of Regents, by resolution, approved the list of nominations and by special resolution renominated to the American Board of Internal Medicine Dr. Walter L. Palmer.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

THE AMERICAN COLLEGE OF PHYSICIANS
ABSTRACT OF MINUTES, BOARD OF REGENTS
CLEVELAND, OHIO, APRIL 25, 1952

The final meeting of the Board of Regents, during the 33rd Annual Session of the American College of Physicians, convened at 12:30 o'clock, Friday, April 25, 1952, at the Cleveland Public Auditorium, Cleveland, Ohio, with President T. Grier Miller presiding, with Mr. E. R. Loveland acting as Secretary and with the following in attendance:

T. Grier Miller	*President*
LeRoy H. Sloan	*President-Elect*
Charles F. Moffatt	*Second Vice President*
Richard A. Kern	*Secretary-General*
A. B. Brower	
Alex. M. Burgess	
George H. Lathrope	
Cyrus C. Sturgis	
Asa L. Lincoln	
J. Owsley Manier	
Walter L. Palmer	
Edward L. Bortz	
Herbert K. Detweiler	
Harold H. Jones	
Howard P. Lewis	
Dwight L. Wilbur	
Charles A. Doan	*Chairman*, Board of Governors

Guests:

Howard Wakefield	Governor for Northern Illinois
Chester A. Wilkins	Executive Director, Chicago Convention Bureau
W. Fred Puffer	National Convention Manager, Chicago Convention Bureau
MacLellan E. King	Director of Sales, The Conrad Hilton Hotel, Chicago

President Miller, instead of proceeding with the formal Agenda for this meeting, gave representatives from Chicago an opportunity to present an invitation to the College for its 1954 meeting place. Dr. LeRoy H. Sloan, President-Elect, Dr. Howard Wakefield, Governor for Northern Illinois, Mr. Chester A. Wilkins, Executive Director of the Chicago Convention Bureau, and Mr. MacLellan E. King, Director of Sales of the Conrad Hilton Hotel, presented, respectively, invitations on behalf of the medical institutions and the medical profession, the civic organizations and the hotel having facilities to accommodate the College. President Miller thanked them and stated that action would be taken later in the meeting, whereupon Mr. Wilkins and Mr. King retired.

The Secretary reviewed the Minutes of the preceding meeting of the Board of Regents, the abstract being accepted by resolution.

Dr. A. B. Brower introduced the subject of group health and accident and/or professional liability insurance for members of the College. He moved the adoption

of a resolution that the Board of Regents approve in principle the policy that it is interested in sponsoring group insurance for its members, directing, first, a full study of the subject by a duly appointed Committee. The motion was seconded by Dr. Howard P. Lewis, and carried.

Dr. Richard A. Kern, Secretary-General, read the original version of the "Interpretation" of the new By-Laws regarding term of Associateship and then presented a revision clarifying certain points, as worked out by Dr. Maurice C. Pincoffs (this "Interpretation" has already been published to all members), and the revision was officially accepted by resolution.

Mr. E. R. Loveland, Secretary, presented a communication from the Chairman of the Conference Committee on Graduate Training in Medicine, requesting the appointment of two Alternates to take the place of the American College of Physicians' representatives on that Committee, in the event that one or both of them might be unable to attend meetings. A resolution was adopted instructing the President to appoint such Alternates. (Subsequently, President Miller appointed Dr. Richard B. Capps, F.A.C.P., Chicago, as the Alternate for Dr. Howard Wakefield, and Dr. Sinclair H. Armstrong, Jr., F.A.C.P., Chicago, as the Alternate for Dr. LeRoy H. Sloan.)

For matter of record, Secretary Loveland reported that President Miller had appointed Governor Edward C. Klein, Jr., of New Jersey, as the official College representative at the inauguration of Lewis Webster Jones as President of Rutgers University.

Dr. Alex. M. Burgess, Chairman, presented the following report for the Committee on the Annals of Internal Medicine:

"Your Committee met on Monday, April 21, 1952. There were present Doctors Palmer and Burgess. The Editor, Dr. Pincoffs, attended the meeting, as did also Mr. Frank Shanbacker of the College Staff.

"1. *Circulation and Finances:*

Increase in the circulation of the ANNALS, now exceeding 15,300 copies, and the increased net profit for the year 1951, $65,373.36 with comparison with previous figures and also the facts regarding the special issue, 'The Acute Radiation Syndrome,' are noted in the Agenda prepared by the office of the Executive Secretary and appended to this report (Attachment A). The Committee wishes to call especial attention to the fact that the net profit in 1951 exceeded that of the previous year by almost $8,000.00, and represents a figure which may well justify the extra expenses involved in making certain changes in the physical aspect of the ANNALS, which have been under consideration.

"2. *Action on Previous Recommendations:*

The report of the Editor to this Committee (Attachment B) and the Progress Report on Recommendations furnished by the Executive Secretary (Attachment A, paragraph II) furnish information regarding the action taken on the eight recommendations presented in the progress report of this Committee and adopted by the Board of Regents in November, 1951. This information may be summarized as follows:

"(a) The recommendation favoring a reduced subscription rate, $7.00 per annum, for medical students, internes and hospital residents has been put into effect.

"(b) The recommendation concerning Dr. McHardy's inquiry regarding the propriety of publication of material based on A.C.P. Postgraduate Courses in reputable journals other than the ANNALS, which recommendation was to the effect that Dr. McHardy should be notified that there was no objection to such publication, has been carried out.

"(c) Concerning the recommendation 'that every effort be made to advance the date of delivery of the journal to its subscribers each month until publication of the first day of the month is achieved,' the Editor reports progress. He points out clearly in his report the difficulties that must be overcome, both in the printer's establishment and in the Executive Office. It is obvious to the Committee that this goal of publication on the first of the month cannot be reached quickly, and the Committee regards the statement of the Editor that by the end of the year publication on the tenth of the month will probably be attained as very auspicious.

"(d) In regard to the fourth recommendation that two young men be added to the staff as Assistant Editors, the Committee has to report that the Editor has suggested an alternate plan, which to him appears preferable. It is the selection of four or five young men, each expert in a particular field, to act as Consulting Editors. Reference is made to the Editor's report for a more detailed discussion of this plan. The additional sum of $1,000.00 needed to pay honoraria to each of these consultants for each piece of work completed has already been voted by the Board of Regents to be added to the budget of the Editor's Office. It is the opinion of this Committee that this new plan, as suggested by the Editor, is preferable to the one previously proposed.

"(e) The recommendation concerning the authorization of the Editor to publish additional original articles and case reports in each issue in order to reduce the delay between the receipt of articles and their publication has been implemented with the excellent results shown in the graph prepared in the Editorial Office. This shows a reduction in this delay from an average of over sixteen months in January, 1951, to six months in June, 1952.

"(f) In regard to the matter of improving the halftone reproductions in the ANNALS, which will necessitate the use of a considerably more expensive paper, your Committee can report that the Executive Secretary has gone to great pains to study this matter and that the Committee was furnished with samples of identical pages with illustrations produced on the paper now in use (45 lb. stock) and on a heavier stock (55 lb.). Samples of the 70 lb. glazed paper used in the *American Journal of Medicine* were also furnished. It was estimated that the use of the higher grade paper (55 lb.) would involve a yearly increase in the cost of about $10,800.00 per year. In comparing the printing and reproduction of roentgenograms on the two types of paper, the Committee is of the opinion that the results obtained by the use of the heavier paper are distinctly superior and that such an improvement is definitely needed. Further detailed discussion is given to the 'Progress Report on Recommendations' furnished by the Executive Secretary (Attachment A, paragraph II-e).

"As the Editor is not satisfied that all information needed in this matter has been obtained, it seems wise, as he suggests, to postpone a definite decision at this time.

"(g) Regarding a change in the format of the ANNALS, this too has been extensively studied, and the Committee was furnished with many different types of cover samples. It seems wise to the Committee to postpone the decision in this matter also until further study has been made.

"Of the samples presented, the one marked No. 1 (in the files of the Executive Office) seems to the Committee to be the best. This is of a pleasant green

color, with a dignified type similar to that on the present Journal, with the Seal of the College shown in gold, and the Contents on the front cover.

"3. *Appointment of an Editorial Board:*

In discussing the selection of the group of Consulting Editors with the Editor, the idea was advanced that it might be well to replace the present group of Associate Editors and the Committee on the Annals of the Board of Regents by an active Editorial Board. This group would include the Consulting Editors and would serve as a Committee responsible for directing policy and administration and supervising the quality of publications in the ANNALS. The membership of this Board should rotate and the term of each member be limited, with the possibility of reappointment so that those members who are active as Consulting Editors could be reappointed as might be desirable.

"4. *Recommendations:*

"(1) It is recommended that decision regarding changes in the physical form of the ANNALS, both regarding the quality of paper used and the format of the Journal, be postponed until further studies have been made, with the intention that these matters shall be settled at the meeting of November, 1952.

"(2) It is recommended that the Editor be authorized to select four or five Consulting Editors to aid him in the evaluation of articles and in such other ways as he may determine, these physicians to be paid a suitable honorarium for each piece of work completed.

"(3) It is recommended that the establishment of an Editorial Board to replace the present Associate Editors and Committee on the ANNALS of the Board of Regents, as described in paragraph 3, be considered further and that a decision in this matter be made at the meeting of November, 1952.

"5. *Acknowledgments:*

The courtesy and help of the Editor and the Executive Secretary and his staff is gratefully acknowledged and the very creditable progress that they have made in carrying out the recommendations of this Committee is appreciated."

This report was formally accepted by resolution.

Secretary Loveland read the following report from Dr. George Morris Piersol, Chairman of the Committee on Technical Exhibits:

"The Committee on Exhibits met at 10:30 a.m. on April 21 at the Public Auditorium and proceeded to inspect the Commercial Exhibits. The entire Committee was present, including Dr. Garfield G. Duncan, Dr. Thomas Klein and Dr. George Morris Piersol, Chairman.

"In the course of the morning the entire Committee visited all the booths, and in many instances signed cards indicating that they had inspected the exhibit in question. It is the opinion of the Committee that the Technical Exhibits of the Thirty-third Annual Session of the American College of Physicians, held in Cleveland, Ohio, April 21–25, 1952, is a worth while and educational feature of the Session. The exhibitors chiefly represent recognized pharmaceutical houses, best known publishers of medical books and a few other groups whose products are of interest to internists. No exhibits were observed which were undignified or unethical. The exhibitors were uniformly courteous, reasonable in their claims and intelligent when questioned about their products. A couple of exhibits were noted in which the material exhibited might be regarded as more appropriate for a group of general practitioners than a body of physicians dedicated entirely to Internal Medicine. At the time when the exhibits were

inspected a satisfactory number of members of the College were going through the exhibits. The exhibitors, as a group, expressed satisfaction that there was a Committee of the College interested in commercial medical exhibits, and were appreciative of the Committee's visit.

"In the afternoon of Monday, April 21, the Committee, as well as the President, President-Elect, the Executive Secretary, met with the group of exhibitors in an informal meeting and discussed various aspects of the Commercial Exhibits, particularly in relation to the American College of Physicians. A number of constructive suggestions were forthcoming. It is the feeling of the Committee that such a meeting with the exhibitors is well worth while and might well be made a routine procedure.

"The Committee on Exhibits is charged not only with the inspection of the Exhibits at the Annual Sessions, but also with the supervision of the advertising that appears in the ANNALS OF INTERNAL MEDICINE. All products that are advertised are passed upon by the Committee and none is accepted for publication in the Journal without the unanimous approval of your Committee. The Committee also passes upon the requests from exhibitors for space at the Annual Sessions."

The above report, by resolution, was accepted.

Secretary Loveland read a letter from Dr. Reginald Fitz, Chairman of the Committee to prepare a revision of the Fellowship Pledge, stating that his Committee had been unable to present a specific revision, and that in view of the fact that it could not be utilized until 1953, the Committee would make its recommendations before the next meeting of the Board of Regents in November.

President Miller requested a report from the Board of Governors, through its Chairman, Dr. Charles A. Doan:

DR. CHARLES A. DOAN: "Mr. President, such matters include:

"The Board of Governors by unanimous vote, lacking one, voted against making certification a prerequisite for Associateship, which is a reversal of our recommendation by the same number of votes a year ago.

"Dr. J. Murray Kinsman has been reappointed by the Board of Governors for another term of three years on the Committee on Credentials.

"The Board of Governors revised the name of the Advisory Committee on Postgraduate Courses to 'Committee on Postgraduate Courses'; the personnel of this Committee for the next year consisting of Dr. Thomas M. McMillan, continuing as Chairman, Dr. Irving S. Wright, appointed as Vice Chairman, Doctors Charles M. Caravati, Stacy R. Mettier and Karver L. Puestow.

"The Board of Governors, through its Chairman, appointed Dr. Carter Smith, Chairman, Dr. Lemuel C. McGee and Dr. Robert B. Radl as a Committee to study a proposal for the issuance of some recognition or type of certificate of service for retiring Governors. It was pointed out in the meeting by Dr. Radl that there is nothing more than a cursory expression of appreciation to Officers, Regents and Governors when they retire from office, and that some certificate or some endorsement on the Fellowship Certificate be added, indicating the type and dates of service. It was suggested that the Chairman of the Board of Governors bring this to the attention of the Board of Regents for their consideration.

"The Board of Governors also refers the problem of membership eligibility of noncitizens of Hawaii and Canada. Our Governors in those areas report there are adequately trained internists there, especially in Western Canada and Hawaii, where citizenship, as in Hawaii, is not available, or, as in some Provinces of Canada, is long delayed, and yet where membership in the College would be desirable. The point was made that some of the young British graduates who have come to Canada, under a new regulation that has been made in the Dominion, are not eligible for citizenship for a prolonged period, longer than formerly. It was pointed out by our Governor for Hawaii that some very worthy and well qualified physicians, because of race and point

of derivation or bound under present laws, can never qualify as citizens and, thus, would be excluded from College membership. Therefore, Governors from these respective areas ask that there be considered action which would remove us from the allegation of racial discrimination and that the Governors in these areas, plus other Fellows of the College, be permitted to recommend for consideration by the Committee on Credentials men who do not strictly meet the citizenship requirement in North American countries. The present policy is to consider for membership citizens only of North American countries and their dependencies."

PRESIDENT MILLER: "You have heard Dr. Doan's report. The only matter that requires any action is the item which refers to citizenship of certain persons in Hawaii and Canada. As I understand it, this matter can be settled by the Board of Regents, for it does not necessarily appear in the By-Laws of the College."

DR. CHARLES F. MOFFATT: "Mr. Chairman, as far as Canada is concerned, I believe that as the law now stands, a man has to be a resident five years before he can become a citizen. That difficulty will apply more to the West, where most young men go. I do not see any reason why we should depart from the law of the country in that they must be there five years before they can become citizens. They can properly wait until they are eligible for certification or fellowship, either in the Royal College or the American College. I think it would be a mistake to alter our regulations in any way as far as Canada is concerned."

DR. HERBERT K. DETWILER: "Mr. President, with regard to these British individuals and, indeed, some of the DP's from Central Europe, the Royal College of Physicians of Canada, through their Credentials Committee, does allow them to come up for examination if they are otherwise qualified without waiting five years. They do, unofficially or informally, wait two or three years, but not for five years."

PRESIDENT MILLER: "I suspect the problem is much more important so far as Hawaii is concerned, because there, unless a person were born in Hawaii, are some, particularly Japanese, who can never become citizens of the United States. Governor Larsen referred to one very excellent Japanese physician who came to Hawaii perhaps when six months old, but will never be able to become a citizen of the United States, yet our members in Hawaii would like to have him as a member of this College."

DR. LEROY H. SLOAN: "Mr. President, I think this is a very important matter, and I move that it be deferred for the meeting in November and studied in the meantime; that it be referred to the Committee on Credentials in consultation with the Executive Committee."

. . . The motion was seconded, put to vote and carried. . . .

At this point the President proceeded with the regular Agenda of elections of the Secretary-General and Treasurer and the appointment of Committees. In accordance with regulations of the By-Laws, Dr. Richard A. Kern was re-elected Secretary-General and Dr. William D. Stroud was re-elected Treasurer.

In accordance with provisions of the By-Laws, or regulations of the Board of Regents, the following Committees were appointed for 1952–53:

EXECUTIVE COMMITTEE

T. Grier Miller, Philadelphia, Pa., *Chairman*
LeRoy H. Sloan, Chicago, Ill.
Richard A. Kern, Philadelphia, Pa.
William D. Stroud, Philadelphia, Pa.
A. B. Brower, Dayton, Ohio
Reginald Fitz, Boston, Mass.
Walter L. Palmer, Chicago, Ill.
Maurice C. Pincoffs, Baltimore, Md.
Cyrus C. Sturgis, Ann Arbor, Mich.

COMMITTEE ON THE ALFRED STENGEL MEMORIAL AWARD

Wallace M. Yater, Washington, D. C., *Chairman*
Alex. M. Burgess, Sr., Providence, R. I.
Chester S. Keefer, Boston, Mass.
John Minor, Washington, D. C.
Robert Wilson, Jr., Charleston, S. C.

Ex Officiis:

T. Grier Miller, Philadelphia, Pa.
Richard A. Kern, Philadelphia, Pa.

COMMITTEE ON ADVERTISEMENTS AND COMMERCIAL EXHIBITS

George Morris Piersol, Philadelphia, Pa., *Chairman*
Garfield G. Duncan, Philadelphia, Pa.
Thomas Klein, Philadelphia, Pa.

COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE

Alex. M. Burgess, Sr., Providence, R. I., *Chairman*	(1953)
Howard P. Lewis, Portland, Ore.	(1955)
Walter L. Palmer, Chicago, Ill.	(1954)

COMMITTEE ON CONSTITUTION AND BY-LAWS

Reginald Fitz, Boston, Mass., *Chairman*	(1954)
Harold H. Jones, Sr., Winfield, Kans.	(1953)
Maurice C. Pincoffs, Baltimore, Md.	(1955)

COMMITTEE ON CREDENTIALS

From the Board of Regents	George Morris Piersol, Philadelphia, Pa., *Chairman*	(1954)
	George H. Lathrope, Morristown, N. J.	(1953)
	J. Owsley Manier, Nashville, Tenn.	(1955)
From the Board of Governors	J. Murray Kinsman, Louisville, Ky.	(1955)
	Lemuel C. McGee, Wilmington, Del.	(1953)
	Robert Wilson, Jr., Charleston, S. C.	(1954)

COMMITTEE ON EDUCATIONAL POLICY

Marion A. Blankenhorn, Cincinnati, Ohio, *Chairman*
Edward L. Bortz, Philadelphia, Pa.
Harold H. Jones, Sr., Winfield, Kans.

COMMITTEE ON FELLOWSHIPS AND AWARDS

Cyrus C. Sturgis, Ann Arbor, Mich., *Chairman*
Charles A. Doan, Columbus, Ohio
William C. Menninger, Topeka, Kans.
Wesley W. Spink, Minneapolis, Minn.
Wallace M. Yater, Washington, D. C.

COMMITTEE ON FINANCE

A. B. Brower, Dayton, Ohio, *Chairman*	(1953)
Herbert K. Detweiler, Toronto, Ont., Can.	(1955)
Walter L. Palmer, Chicago, Ill.	(1954)

COMMITTEE ON MASTERSHIPS

Walter B. Martin, Norfolk, Va., *Chairman*
John Minor, Washington, D. C.
Charles F. Moffatt, Montreal, Que., Canada

COMMITTEE ON MILITARY AFFAIRS

Richard A. Kern, Philadelphia, Pa., *Chairman*
F. Dennette Adams, Boston, Mass.
William S. McCann, Rochester, N. Y.
Elbert L. Persons, Durham, N. C.
Benjamin H. Rutledge, Baltimore, Md.

COMMITTEE ON NOMINATIONS

Walter L. Palmer, Chicago, Ill., *Chairman*	(Regent)
Paul F. Whitaker, Kinston, N. C.	(Regent)
Ray F. Farquharson, Toronto, Ont., Can.	(Governor)
Leslie R. Kober, Phoenix, Ariz.	(Governor)
A. McGehee Harvey, Baltimore, Md.	(Fellow-at-large)

COMMITTEE ON POSTGRADUATE COURSES

Thomas M. McMillan, Philadelphia, Pa., *Chairman*
Irving S. Wright, New York, N. Y., *Vice Chairman*
Charles M. Caravati, Richmond, Va.
Stacy R. Mettier, San Francisco, Calif.
Karver L. Puestow, Madison, Wis.

COMMITTEE ON PUBLIC RELATIONS

Edward L. Bortz, Philadelphia, Pa., *Chairman*	(1954)
Asa L. Lincoln, New York, N. Y.	(1956)
LeRoy H. Sloan, Chicago, Ill.	(1953)
Dwight L. Wilbur, San Francisco, Calif.	(1955)

Ex Officio:

T. Grier Miller, Philadelphia, Pa.

CONFERENCE COMMITTEE ON GRADUATE TRAINING IN MEDICINE

LeRoy H. Sloan, Chicago, Ill., *Chairman*
Howard Wakefield, Chicago, Ill.

Alternates:

S. Howard Armstrong, Jr., Chicago, Ill.
Richard B. Capps, Chicago, Ill.

CONSULTING COMMITTEE ON ANNUAL SESSIONS

T. Grier Miller, Philadelphia, Pa., *Chairman*
Hilton S. Read, Atlantic City, N. J.
Maurice C. Pincoffs, Baltimore, Md.
Roy W. Scott, Cleveland, Ohio
William S. Middleton, Madison, Wis.
Ralph A. Kinsella, St. Louis, Mo.

HOUSE COMMITTEE

William D. Stroud, Philadelphia, Pa., Chairman
Charles L. Brown, Philadelphia, Pa.
Thomas E. Machella, Philadelphia, Pa.

JOINT COMMISSION ON THE ACCREDITATION OF HOSPITALS

LeRoy H. Sloan, Chicago, Ill., *Chairman*	(1954)
Alex. M. Burgess, Sr., Providence, R. I.	(1955)
William S. Middleton, Madison, Wis.	(1953)

American Council on Rheumatic Fever

William D. Stroud, Philadelphia, Pa.
Russell L. Cecil, New York, N. Y.

The Joint Committee for the Coördination of Medical Activities was discontinued. Nominations to the American Board of Internal Medicine had been provided for in a previous meeting. A resolution was adopted authorizing the President to appoint the General Chairman of the 34th Annual Session, to be held in Atlantic City in 1953.

After extended discussion and presentation of information, Chicago was chosen as the site of the 1954 Annual Session, and the dates of April 5–9 were selected and approved.

President Miller: "I am very much interested in some further study of the status of Associateship in the College and other criteria for Fellowship. It has occurred to me that it might be interesting, during the coming year, if we could secure adequate facilities to study a number of conditions. For instance, to classify our present Fellowship on the basis of those who are teachers, those who are in research, those who are practitioners, those who are interested in public health activities, or other administrative work. It would be interesting to know how many Fellows of the College and Associates, too, are connected with hospitals or with medical schools, how many with private clinics, etc. It would be interesting to know how many of our members have teaching positions in medical schools, to know how many are Professors, Associate Professors, Assistant Professors, etc.; also to know how many men occupying these ranks are not Fellows of this College.

"It might be worth while to find out, too, to what extent our present criteria for Fellowship are interfering with the admission to the College of certain important clinical men in the country. I am asking the Board if it would be agreeable to have a committee to make some such studies during the coming year. Obviously, the committee cannot have numerous meetings and do this work itself, but I think our Central Office could carry out this study—if necessary, add an additional person to the staff."

Dr. Brower: "Mr. President, I think there would be a lot of virtue in what you are talking about. There are unquestionably a number of excellent internists, teachers, professors who are not members of the College, and both they and the College would be benefited by membership. Often these people are hesitant about asking to be proposed. It might be a good idea for some of those duties to be given to the Governor and his special committee."

Dr. George H. Lathrope: "Mr. President, inquiries could be made to the Deans of the medical schools, perhaps, as to why these men are not Fellows. Is it not your desire to find out why certain numbers of them are not in the College?"

Dr. Walter L. Palmer: "Do you want authorization for a committee to study this matter?"

President Miller: "I certainly would like very much to have such authorization. I do not think any of us can say at the moment exactly what the outline of the program should be. I personally would think it desirable to allow the Finance Committee or Treasurer to appropriate a certain amount of money to assist in this study, because it seems to me that it is going to carry more work than the Executive Secretary's Office can handle without additional help."

Dr. Palmer: "I am very glad to move you be authorized to appoint such a Committee. Do we need to include in the recommendation any provision for funds? The Executive Secretary's Office is authorized to hire such employees as may be necessary to conduct the work of the office."

Secretary Loveland: "We have a specific budget, but it is based upon the current employees and the anticipated needs at the time of its adoption, November, 1951. It does not provide for employment of additional personnel. The current proposal

may be a comparatively small job which we could do with our present staff, or it might turn out to be a very extensive study that would require additional personnel. That will depend on what the Committee asks for."

DR. PALMER: "It would be best to include in my motion a recommendation that if additional funds are required for the study, the matter shall be referred to the Executive Committee for additional appropriation."

. . . The motion was seconded by Dr. Cyrus C. Sturgis, put to vote and carried, and President Miller subsequently appointed a *Committee on Membership*, consisting of:

Richard A. Kern, Philadelphia, Pa., *Chairman*
Charles A. Doan, Columbus, Ohio
Walter B. Martin, Norfolk, Va.
Walter L. Palmer, Chicago, Ill.
LeRoy H. Sloan, Chicago, Ill.

Dr. Walter L. Palmer referred to the report of Dr. Marion A. Blankenhorn and the Committee on Educational Policy, which was tabled at a previous meeting, and moved that Dr. Blankenhorn be notified that the Board of Regents is not clear as to the intent of his motions at the previous meeting and that the Board trusts he will prepare a more specific recommendation to the Board of Regents in November.

Adjournment.

Attest: E. R. LOVELAND
Secretary

MINUTES OF THE BOARD OF GOVERNORS
CLEVELAND, OHIO, APRIL 23, 1952

The second meeting of the Board of Governors of the American College of Physicians, held during the 33rd Annual Session, was convened at 12:30 o'clock, April 23, 1952, at the Cleveland Public Auditorium, Cleveland, Ohio, Dr. Charles A. Doan, Chairman, presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

Leland Hawkins, Los Angeles ..... California (Southern)
Ward Darley, Denver ..... Colorado
*John C. Leonard, Hartford ..... Connecticut
Charles H. Drenckhahn, Urbana ..... Illinois (Southern)
James O. Ritchey, Indianapolis ..... Indiana
William C. Menninger, Topeka ..... Kansas
Chester S. Keefer, Boston ..... Massachusetts
Joseph D. McCarthy, Omaha ..... Nebraska
Edward C. Reifenstein, Sr., Syracuse ..... New York (Western)
Wann Langston, Oklahoma City ..... Oklahoma
*Edward L. Bortz, Philadelphia ..... Pennsylvania (Eastern)
Charles W. Morton, Pittsburgh ..... Pennsylvania (Western)
William C. Chaney, Memphis ..... Tennessee
Fuller B. Bailey, Salt Lake City ..... Utah
Nils P. Larsen, Honolulu ..... Hawaii
Herbert K. Detweiler, Toronto ..... Ontario
Cornelius DeW. Briscoe, Panama ..... Republic of Panama and the Canal Zone
Arless A. Blair, Fort Smith ..... Arkansas
Stacy R. Mettier, San Francisco ..... California (Northern)
Benjamin F. Wolverton, Cedar Rapids ..... Iowa
Thomas Findley, New Orleans ..... Louisiana
Douglas Donald, Detroit ..... Michigan
Ralph A. Kinsella, St. Louis ..... Missouri
Harry T. French, Hanover ..... New Hampshire
Edward C. Klein, Jr., South Orange ..... New Jersey
Elbert L. Persons, Durham ..... North Carolina
Robert B. Radl, Bismarck ..... North Dakota
*Louis I. Kramer, Providence ..... Rhode Island
Robert Wilson, Jr., Charleston ..... South Carolina
Ellsworth L. Amidon, Burlington ..... Vermont
Charles M. Caravati, Richmond ..... Virginia
George H. Anderson, Spokane ..... Washington
Paul H. Revercomb, Charleston ..... West Virginia
Jose J. Centurion, Havana ..... Cuba
*D. O. Wright, Birmingham ..... Alabama
Leslie R. Kober, Phoenix ..... Arizona
Lemuel C. McGee, Wilmington ..... Delaware
William C. Blake, Tampa ..... Florida
Carter Smith, Atlanta ..... Georgia
Richard P. Howard, Pocatello ..... Idaho

* Alternate Governors.

Howard Wakefield, Chicago	Illinois (Northern)
J. Murray Kinsman, Louisville	Kentucky
Richard S. Hawkes, Portland	Maine
R. Carmichael Tilghman, Baltimore	Maryland
Laurance J. Clark, Vicksburg	Mississippi
Harold W. Gregg, Butte	Montana and Wyoming
Walter I. Werner, Albuquerque	New Mexico
Irving S. Wright, New York	New York (Eastern)
Charles A. Doan, Columbus	Ohio
Merl L. Margason, Portland	Oregon
Karver L. Puestow, Madison	Wisconsin
Rafael Rodriguez-Molina, San Juan	Puerto Rico
*J. F. Elliott, Edmonton	Alberta and British Columbia
Charles H. A. Walton, Winnipeg	Manitoba and Saskatchewan
*Dan C. Ogle	United States Air Force
George E. Armstrong	United States Army
*R. A. Bell	United States Navy
*Myron D. Miller	United States Public Health Service
Joel T. Boone	Veterans Administration

Guests:

Angel Vieta, Havana, Cuba	
T. Grier Miller, Philadelphia	President-Elect

The Secretary reviewed the Minutes of the preceding meeting, which were approved as read.

Chairman Charles A. Doan: "I will ask Dr. Edward L. Bortz, Chairman of the Committee on Constitution and By-Laws, to present the amendment that is to be presented at the Annual Business Meeting on April 24, 1952."

. . . Dr. Edward L. Bortz read Article VII, Section 4, of the By-Laws, inserting the changes authorized by the Board of Regents, increasing the maximal Associate term to ten years instead of five years, and, by resolution, the amendment was approved by the Board of Governors. . . .

. . . The Secretary then read the interpretation as previously approved by the Board of Regents and published in its Minutes. . . .

Chairman Doan: "In amplification of these recommendations, what we are trying to do is to be fair to those who within the current year have had their Associateship terminated, in terms of a five-year period, and who either would have been dropped, or are being dropped, because of that, or who have resigned in anticipation of not having been able to fulfill the requirements for Fellowship within five years. We are trying to give an extension of time with a minimum of red tape for these individuals in terms of the change in our general procedure with reference to the years of Associateship, in order that they shall have the remainder of a ten-year period in which to qualify.

"It has been recommended and approved by the Board of Regents that this interpretation at this time would do the least injustice to all concerned. It will be necessary for the candidate himself, in writing, to request this extension, with some statement, perhaps, of his feeling that he will be able to meet the Fellowship requirements in the time that has been given in extension; that his original proposer in his community and his original seconder shall give it consideration, and that the appropriate Governor

* Alternate Governors.

shall endorse his extension, and the application then will go to the Credentials Committee and the Board of Regents. In other words, this plan gives the candidate reconsideration and re-evaluation, taking the place of formal proposal through the printed form.

"Now, those who accept the fact that they have been dropped, or those who have resigned, but do not make application for reinstatement may, if they prefer, later on be reproposed for a full ten-year term. Such men will have the election of either waiting a year, being reproposed from scratch and being considered all over again, or they can ask for reinstatement now. However, we are not guaranteeing that they will be continued.

"This report has been accepted unanimously by the Board of Regents for submission first to the Board of Governors for approval and then to the College at its Annual Business Meeting on Thursday, April 24, 1952."

Dr. Douglas Donald: "How long a period do these Associates have in which to make their request for reinstatement?"

Chairman Doan: "No limit has been specified, but it was thought that a letter would go out from the Executive Secretary's Office as soon after this meeting as possible. It will be sent to the candidate, with a copy to his proposer, and a copy to the Governor, so that they will know the candidate has had advice, explaining to him his choice in terms of the action taken. As to the time limit, I presume an interpretation will be made by the Executive Secretary, or, perhaps, it will be held open until a response is received, one way or the other, from the individual."

Secretary E. R. Loveland: "I would think that this should be done probably within a period of six months, and that after that at the discretion of the Governor in the state from which the candidate comes."

Chairman Doan: "Is there any disposition on the part of the Board of Governors to suggest a time element, which has not thus far been raised by the Regents."

Dr. Edward C. Reifenstein, Sr.: "I move that we approve the recommendations, that is, the interpretation."

Dr. Ralph A. Kinsella: "I second the motion."

Chairman Doan: "Is there discussion?"

Dr. Kinsella: "It seems to me an inconsistency in this action in that if the present expiring five-year Associates are being given this opportunity to rehabilitate, that the next group of Associates should be subjected to about the same type of scrutiny, so that at the end of their five years they would be asked to do something about it."

Chairman Doan: "There will be scrutiny year by year from now on of each Associate, because it has been suggested and approved in principle that there be a running inventory of individual Associates, of their progress, from year to year in the Governors' Office. This information would be furnished to him by those in the community most aware of the Associate's activities there, rather than to have any periodic notification of the progress of time that we now have—it is a matter of custom that the Executive Secretary sends a letter at the end of each year, apprising each Associate of the passing of time, and after three years, particularly, the candidate is notified that he now has the minimum requirements in time for application for Fellowship. It is the intent now that there will be from the Central Office, as well as from the Governors, a contact that will be continuing each year with each candidate, in the hope that we can encourage him to make the progress in his educational environment that the College expects."

Dr. Kinsella: "But he couldn't be dropped for ten years."

Chairman Doan: "If the amendment is adopted at the Annual Business Meeting, that is right."

Dr. Elbert L. Persons: "My understanding of paragraph three is not quite clear. I am thinking of an Associate who had his term extended, so that he was an Associate

for six years and then had to resign. If that man comes back, under this provision, is his term for ten years from the date of election, or does he get four more years?"

CHAIRMAN DOAN: "A maximum of ten years from the date of election."

DR. PERSONS: "For clarification, are these letters to go out from the Executive Secretary's Office?"

CHAIRMAN DOAN: "The Governor will conduct his own offices as he pleases, but the Executive Secretary's notices will be in addition to that. There still is autonomy in terms of each Governor's Office.

"Is there any desire to make a time limit in which to permit an Associate who would otherwise be dropped now to request reinstatement?"

DR. JAMES O. RITCHEY: "I move that that be a six months' period."

CHAIRMAN DOAN: "A maximum period of six months after the adoption of this amendment."

DR. RICHARD P. HOWARD: "What about those who are reproposed after a year or more—is this ten-year period going to be final?"

CHAIRMAN DOAN: "This matter has no influence on those who are reproposed for Associateship. There is no change in the Constitution or By-Laws with respect to that. Such candidates are completely reconsidered and, if elected, are entitled to a full additional ten-year term."

. . . On motion by Dr. James O. Ritchey, seconded and carried, it was

RESOLVED, that it is the sense of the Board of Governors that any Associate entitled to apply by letter for reinstatement shall do so within a maximum of six months after the adoption of the amendment to the By-Laws. Also, by resolution the interpretation of the amendment, as presented through Dr. Walter L. Palmer's Committtee report, was approved. . . .

CHAIRMAN DOAN: "A year ago we had unanimous action, except one, on the report of the Board of Governors to the Board of Regents, one item which provided that certification by the American Board of Internal Medicine, or by an allied board, shall be a requirement for Associateship. This returned recommendation from the Committee of the Board of Regents was not actually acted upon by the Board of Regents, but referred to us for consideration. I would like to suggest that that raises the question of whether certification shall be required for Fellowship if not for Associateship, or shall certification be a requisite at all for membership in the College?"

DR. KARVER L. PUESTOW: "Mr. Chairman, I move that certification not be a prerequisite for Associateship."

DR. NILS P. LARSEN: "I second the motion."

CHAIRMAN DOAN: "The matter is open for discussion."

DR. STACY R. METTIER: "Mr. Chairman, I have discussed this matter with our members in my area. Most of them are in favor that we use the Board requirements if not for Associateship then certainly for Fellowship. They feel the stimulus the candidates get from the examination offers them a great deal in the way of training in Internal Medicine, and they feel that it helps to maintain our standards."

DR. PUESTOW: "The brevity of this motion had as its object the facilitation of action by this Board, in order that we might proceed with one question at a time. I had in mind that this Board subsequently would adopt another resolution concerning certification for Fellowship, although a few men might be elected to Direct Fellowship without certification."

CHAIRMAN DOAN: "This subject has been discussed by this Board for the past ten years, and a year ago the Board was practically unanimous that certification should be made a part of the requirements for Associateship. The Board further thought that certification for Fellowship might minimize the necessity for essays, clinical theses, etc. On the other hand, the rôle that the College plays in the earlier years of a man's

development was thought to be sufficiently great that it would be very desirable to have younger men still working for their boards actually within the Associateship of the College. If we are truly a College, in terms of our educational objectives, I think there is much to be said for lowering at least that particular hurdle for Associateship."

DR. RITCHEY: "I am essentially in agreement with Dr. Puestow's motion, but how many will be taken in as Associates that probably never will have any chance to qualify as Fellows?"

CHAIRMAN DOAN: "I am not a prophet. It would be pretty difficult to estimate."

SECRETARY LOVELAND: "At present certification is not required for Associateship, but the Credentials Committee requires that the candidate provide proof that he is eligible for admission to the examinations. More than 50% of the Associate candidates are certified at present."

DR. PUESTOW: "Mr. Chairman, in no way does the present motion imply that the standards of the College should be reduced. On the contrary, with the extension of the Associate term to ten years, there would be the implication that the standards for Fellowship would be considerably raised."

. . . The motion was put and carried. . . .

CHAIRMAN DOAN: "At this time we would like a report from the Advisory Committee on Postgraduate Courses, by Dr. Edward L. Bortz, Acting Chairman for Dr. Thomas M. McMillan, Chairman."

DR. BORTZ: "Mr. Chairman, your Committee makes the recommendation that its name 'Advisory Committee on Postgraduate Courses' should be revised to 'Committee on Postgraduate Courses,' because it is an exceedingly active Committee.

"The Committee has a splendid group of courses scheduled for the autumn of 1952 and the spring of 1953. It hopes to get the Postgraduate Bulletin out sufficiently early, so that those who want to decide on courses they wish to take shall have a clear understanding of the content."

. . . Dr. Bortz read the list of courses, repeating that part of the report already recorded in a meeting of the Board of Regents. . . .

DR. BORTZ (continuing): "With those of you who are interested in giving courses in the future, the Committee desires to discuss in greater detail the budgetary setup. Once or twice in the past Directors have expended considerably more than the income provided from their particular courses."

CHAIRMAN DOAN: "I think this Committee is the most important Committee we have in the College, in terms of our educational objectives."

. . . On motion by Dr. Lemuel C. McGee, seconded by Dr. Howard Wakefield, and carried, the recommendations of the Committee with regard to change in name and with regard to courses scheduled were approved, and the report as a whole accepted. . . .

CHAIRMAN DOAN: "We certainly appreciate the activities of the Committee on Postgraduate Courses and would like Dr. Bortz to carry back to Dr. McMillan our appreciation and our best wishes for his rapid return to normal health again.

"I would now like to name the personnel of the Committee on Postgraduate Courses for the coming year:

Dr. Thomas M. McMillan, Chairman, Philadelphia, Pa.
Dr. Irving S. Wright, Vice Chairman, New York, N. Y.
Dr. Charles M. Caravati, Richmond, Va.
Dr. Stacy R. Mettier, San Francisco, Calif.
Dr. Karver L. Puestow, Madison, Wis.

"It also becomes necessary this year to reappoint one of our representatives on the Committee on Credentials. We have three each serving a three-year term, one

term expiring each year. We have Dr. Lemuel C. McGee, whose term expires in 1953, and Dr. Robert Wilson, Jr., whose term expires in 1954. Dr. J. Murray Kinsman is finishing his first term, and with the approval of the Board of Governors, I would like to nominate Dr. Kinsman to succeed himself for another three-year period."

. . . On motion by Dr. Elbert L. Persons, seconded by Dr. William C. Menninger, and carried, Dr. J. Murray Kinsman was elected. . . .

CHAIRMAN DOAN: "Thank you, Dr. Kinsman, for the fine work you have been doing in the past on this very important Committee.

"Dr. Robert B. Radl, of Bismarck, N. D., has a recommendation and discussion to bring before this Board."

DR. ROBERT B. RADL: "There have been in the past many Governors who have served the College well and now are ex-Governors with no particular distinction or prerogatives. The thought came to me that the College might have a certificate of appreciation, or something that it will issue to retiring Officers, Regents and Governors. The actual details or mechanism of how this would be carried out may be discussed, but I have the thought that perhaps it should be a certificate. In discussing this with Dr. Doan, he had some other ideas, such as a gavel. I simply bring it up, thinking that this Board could voice an opinion at this meeting and adopt something that could become effective in the fairly near future."

CHAIRMAN DOAN: "The retiring President is presented with a gavel. So far as I know, the retiring Governor or Regent receives nothing, except a warm handshake and a letter of appreciation from the Executive Secretary."

DR. CARTER SMITH: "Mr. Chairman, at the present time we have quite a few certificates on our walls, and instead of adding, I suggest we ask the Secretary to have inscribed on the bottom of our present College certificate the appropriate certification."

CHAIRMAN DOAN: "It would be in the nature, perhaps, of a series of visas added to one's Fellowship Certificate. I suppose we can only act in terms of Regents and Officers; we couldn't vote that for ourselves. Perhaps, it is merely a suggestion for the Regents, or, perhaps, we can legislate for the Board of Governors and make the suggestion for the Regents, as far as they are concerned."

DR. CORNELIUS DEW. BRISCOE: "I would think we could have something more appropriate for use when we meet. We could have a small button or emblem, some insignia to wear to the Annual Sessions."

DR. SMITH: "I would move that the terms of office be entered on the Governor's Fellowship Certificate by the Central Office, following the Governor's completion of his service."

DR. RADL: "I do not think we should be going too fast on this. We should think about it longer, and the Regents should have a chance to consider the matter also."

DR. LEMUEL C. MCGEE: "Dr. Smith's is one of three ideas we have received. Isn't it better to have the men think about this and report back whether it should be a lapel button, certificate or a special award? If Dr. Smith would accept the amendment that these three ideas and others of this type be considered by a committee, a report could be brought back to us and suggestions passed along to the Board of Regents."

DR. SMITH: "There has been no second to my motion, and I think the simplest thing to do is to withdraw it."

CHAIRMAN DOAN: "Thank you, Dr. Smith. Would you then second the suggestion of Dr. McGee, namely, that a committee be given the responsibility of studying this question over a year and bringing back a recommendation then?"

DR. SMITH: "Yes."

. . . The motion was put and carried. . . .

CHAIRMAN DOAN: "A committee shall be appointed, and we shall notify you later.

"The list of current and future Regional Meetings and regional activities has been distributed. Will the Secretary say a word?"

SECRETARY LOVELAND: "This report on Regional Meetings for 1951–52 and meetings already scheduled in 1953, along with attendance figures where known, has been prepared for your information. The greatest problem in my office is that of getting the particular guest you want at your Regional Meeting. President Pincoffs and President-Elect Miller have traveled far and near this past year to attend a given number of these meetings, but, obviously, they cannot go to all. We would like you to consider sometimes asking other Officers, such as the Vice Presidents, the Secretary-General or a Regent. Many have already approached Dr. Miller at this Session concerning his attendance at their forthcoming Regional Meeting this coming year. He cannot come to all of them, but he and I will try to obtain your choice from other Officers or Regents. The important thing is to let us work as far in advance as possible in setting up your Regional Meetings. It requires five or six days in my office to print the programs and to get them into the mails. I think you all know that my office prints all of your forms, your programs, tickets, announcements, etc., and pays the postage. Also, that we pay the travel expenses of the Officer or Regent who is sent to your meeting."

DR. CHARLES H. A. WALTON: "I have a question to present to the Board. In my particular area, Manitoba and Saskatchewan, the regular Regional Meeting does not seem to be indicated. We are isolated from other communities and it meant that we were simply lecturing each other, a useless procedure.

"It was suggested by some of our members that we might have a local Postgraduate Course, which would be aimed largely at practitioners, other than the members of the College, because members of the College would constitute the faculty. In large measure this would be quite different from the courses normally put on, in that the members of the College would be doing this essentially for other practitioners. It would not have a very wide interest, because of distance, but it would serve a useful purpose in our area. I discussed this with Mr. Loveland, and he believed we might properly arrange such a Postgraduate Course with our University."

CHAIRMAN DOAN: "In many instances the final day of a Postgraduate Course given for Fellows and Associates has been arranged as the Regional Meeting for the area. It has worked quite successfully. It is easily arranged, and it is appropriate to carry it out officially through the Executive Secretary's Office. There would be no objection to your doing that in terms of a combination of a Postgraduate Course and Regional Meeting. You may do it in any fashion that meets your needs."

DR. BORTZ: "Mr. Chairman, this is an excellent suggestion, and it brings two groups together; the visitors from out of the region coming to take the course have an opportunity to meet some of the Fellows. If you were going to put on a course possibly in conjunction with the University and make it a course with a dual sponsorship—I might say that it has been the policy of the College to have it under the auspices of the American College of Physicians with the coöperation of the University. For example, in a number of states the state university has made overtures that they join forces with the College and have co-sponsorship. The same thing has occurred in regard to county and state medical societies. We think the College should stand alone in sponsorship of any of these courses. I am heartily in favor of developing that idea.

"The programs for the Regional Meetings are excellent opportunities for younger men who are aspiring to Fellowship to present their wares and what they have been working on. In reviewing the programs of speakers in a good many Regional Meetings, in the past five or six years there has often been an all-star aggregation of Professors, sometimes very few of them members of the College. They are brought in in an effort to have an exceedingly strong program. Now, the high quality of work that a good many of our young men are doing at the present time warrants the considera-

tion of their being put on Regional Meeting programs. Then, too, our President and President-Elect, visiting these Regional Meetings, have often selected some of these younger men who did exceedingly good work to present papers at the Annual Meeting. This is an excellent opportunity, and I would suggest that whenever you make your programs for your Regional Meetings you stress heavily the opportunities that are offered for younger men to present papers—men who are sufficiently interested in progress to have the kind of presentation that should be seriously considered."

CHAIRMAN DOAN: "As a matter of actual procedure, if the proposal is an actual Postgraduate Course and sponsored by the College, then it should go through the Committee on Postgraduate Courses, whereas if it were to be a Regional Meeting that would have postgraduate implications, it would go only through the Governor and the Central Office. I think the discrimination and distinction there would be that way. If one wishes to have a Postgraduate Course with the members of the College in that region invited as a substitute for a Regional Meeting, then that would be your decision, Dr. Walton, in terms of communication with Mr. Loveland's office. If you are going to have a Postgraduate Course—with quotations around it—it has to have the consideration and approval of the Committee on Postgraduate Courses.

"Is there any other discussion?"

DR. PUESTOW: "In many instances in the past Postgraduate Courses have been given just before or just after the Annual Session. Likewise, the Committee on Postgraduate Courses has scheduled courses just before some Regional Meetings, making the Regional Meeting the concluding part of the course; such will be the case with the Midwest Regional Meeting in November at Chicago, which will be preceded by an official College course at the Presbyterian Hospital."

CHAIRMAN DOAN: "If no further discussion, I shall proceed to a recommendation that Dr. Elbert L. Persons, of Durham, N. C., has made in writing with reference to the indoctrination of new Governors and the implementation of the activities as they are being developed for the Governors."

DR. PERSONS: "My suggestion is that a sort of a standard operating procedure notebook be gotten up in loose leaf form and furnished to the Governors, outlining the things the Governor shall do and outlining such things as Mr. Loveland has emphasized concerning the services of the Central Office in printing programs, tickets, announcements, etc., for Regional Meetings, how programs are to be handled, etc. I would suggest that this notebook be furnished in duplicate, so that the Governor's secretary may also have a copy.

"It would simply promote standardization of work and make it possible for us to pass on to the next Governor a more satisfactory type of file. It should cover the details of handling proposals for membership and all other duties assigned to the Governor."

CHAIRMAN DOAN: "Mr. Loveland, will you speak to this question?"

SECRETARY LOVELAND: "I have read Dr. Persons' suggestions carefully. I think they are practical and can easily be carried out. A loose leaf notebook of instructions and reminders in brief form of the duties and methods of procedures for Governors—general information, proposal of candidates, conduct of Regional Meetings, duties at the Annual Sessions, and other salient data—can be readily worked up with the assistance of our Office and the advice of the President and the Chairman of the Board of Governors."

DR. ROBERT WILSON, JR.: "I make a motion that we accept the recommendation."

. . . The motion was seconded by Dr. Stacy R. Mettier, and carried. . . .

CHAIRMAN DOAN: "Tomorrow, immediately following the Annual Business Meeting, there will be a meeting of the new Governors who will have been elected for a session of indoctrination and for bringing up to date in terms of the action that has

been taken here. This concludes the agenda of old business and we are ready now for new business."

Dr. Joseph D. McCarthy: "An embarrassing situation arose three or four months ago, which prompts me to call your attention to the fact that our Constitution and By-Laws make no mention, as far as qualifications for Associateship are concerned, with regard to term of residence or establishment. It is true that it is to be found in the small brochure that is put out by the College, but it is entirely a ruling of the Committee on Credentials and the Board of Regents.

"We do have in the Constitution and By-Laws, under 'Qualifications for Fellowship,' a very definite statement that the individual must have had residence at least for three years prior to being recognized for Fellowship. It reads in part, 'if he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of Internal Medicine, or an allied specialty, at a permanent location for at least three years preceding nomination for Fellowship.' I believe there should be added to the By-Laws, under 'Qualifications for Associateship,' the regulations of the Regents that a candidate for Associateship shall have been established in a permanent location for a minimum period of two years, and that this should be added to the By-Laws, Article VII, section (e).

"The reason I have presented this is because one of our Fellows was quite interested in getting a young man in as an Associate. This young man had been in our state three months, and I told him that I thought because of his recent arrival, he would not be qualified for Associateship. He immediately replied that he had looked that up and had found no such statement in the Constitution and By-Laws. He knew it had been published in the small brochure, but because it was not officially in the Constitution and By-Laws, he felt he had a perfect right to propose the candidate. I used my prerogative and refused to endorse the application until the candidate should be permanently established. However, I did peruse the Constitution and By-Laws, and found there are many things that should be contained therein, and others that certainly should be reviewed. I would respectfully request that this Board of Governors suggest to the Regents the possible need for revision of our Constitution and By-Laws. The By-Laws contain nothing as to what the duties of Committees shall be, and there are other missing instructions. I move that the By-Laws be amended, Article VII, Section (1), with an additional paragraph '(e),' 'He shall have been established in a permanent location for a minimum period of two years. The Committee on Credentials shall have discretionary powers to modify this ruling under exceptional conditions.'"

Chairman Doan: "As I understand it, this regulation already exists as an unwritten law."

Secretary Loveland: "The By-Laws provide certain specific requirements, both for Associateship and for Fellowship. The Constitution provides additionally that there may be 'such additional rules as the Board of Regents may from time to time adopt.' The Board of Regents through the years has adopted several additional rules and requirements, such as this residence rule, and while these supplementary requirements are not published in the By-Laws, they are stated in all the literature which concerns the specific criteria for election to membership."

Chairman Doan: "Is there a second to the above motion?"

Dr. Reifenstein: "I second it."

Dr. Stacy R. Mettier: "Many of our men are going to serve in the Armed Forces and will be away for two years, which means it would be five years before they can apply for Associateship. I am wondering if some amendment could be made which would qualify this rule with regard to those in the Armed Forces?"

Dr. Edward C. Klein: "I have had that very experience with some Associate candidates in New Jersey. Some proposers have been annoyed because I could not

endorse a candidate according to the present rules, because the candidate did not have sufficient residency. These proposers asserted that the College is penalizing a man for serving in the Armed Forces. I agreed if the proposer would mention the fact, I would take it into consideration in my endorsement and would present it to the Credentials Committee. In one particular case, in spite of the proposer's demands and my plea for the candidate, the Credentials Committee turned it down, because the candidate did not have sufficient residency."

CHAIRMAN DOAN: "I wonder if it might not be possible, under those circumstances in following a career in the Services, to have some record or endorsement in terms of the accomplishments in the Services of these men, which could be accepted by the Credentials Committee?"

GENERAL GEORGE E. ARMSTRONG: "You will recall that back in Dr. Miley's time, in the Office of the Secretary of Defense, we developed for the Army, Navy and Air Force a diary-sort of a record which the candidate may use when he applies to take one of the board examinations. That same document could be used when the candidate is proposed for Associateship. A record is kept of everything the candidate does, his assignments, etc. His notes are checked from time to time by consultants, which verifies or negates his statements. They are always verified."

CHAIRMAN DOAN: "That is exactly what I had in mind."

DR. MCCARTHY: "I favor a three-year instead of a two-year resident rule. (1) Great stress is being made on screening new men who are coming in as Associates, and it has been stated that if we are going to reduce our problems from that angle, it must be done at the Associate level. That means that at times some men can come to a community, be there for two years, which isn't too long, during which time not enough opportunity has been given to know him; (2) Two years is not sufficiently long to give any assurance that he is going to stay in that community. I have discussed the matter with some of the Regents, some of the members of the Credentials Committee and with members of the Committee on Constitution and By-Laws, and it is felt possibly the same requirement for residence should be made for Associateship as we now have for Fellowship."

CHAIRMAN DOAN: "The amendment to the motion is distinctly in contrast with the intent and form of the original motion, and may the Chair rule that we reserve action on the amendment until we find out whether the original motion is accepted or rejected?"

DR. IRVING S. WRIGHT: "I would accept that. I had in mind the fact that not only Army, Navy and Air Force Medical Officers might be involved, but also young men who are migrating from one medical school to another. Some of these are among the most valuable assets we could have in the College. These men are, by necessity of migration, being penalized. I believe that our Associates should be properly screened within two years of residence in a community."

DR. HOWARD WAKEFIELD: "What Dr. McCarthy illustrated is very sound observation. Yet, it is very important to the College and to the Associates, and I think we should study this further, rather than to make a final decision today. I recommend we refer it to the Regents for their study and then let them come back with the recommendation."

CHAIRMAN DOAN: "This would have to go from us to the Board of Regents as a recommendation."

DR. BENJAMIN F. WOLVERTON: "I would like to speak in opposition to that motion. Not infrequently a man will finish his medical residency and then will stay in at the hospital or medical school where he has taken that residency as clinical assistant or instructor for two or three years and then enter practice somewhere. Now, those men would be valuable candidates to the College, but certainly would be penalized

by such a ruling. Two years' residence for Fellowship is sufficient, and there should not be any time restriction for election to Associateship."

DR. METTIER: "I agree with the motion for two years, but I would like to incorporate an amendment that we give credit to the men who are in the Armed Forces and to the men taking graduate education residencies."

CHAIRMAN DOAN: "It is suggested by Dr. Mettier that we amend the resident period in any one community to the effect that there be considered written comments from the Armed Services, if candidates have served a part of this period of apprenticeship in the Armed Services and there are records available to us as now used by the boards, and that other training and experience, in terms of graduate work at acceptable institutions, be submitted to the Committee on Credentials in support of an earlier consideration of these younger men for Associateship than would otherwise be possible if we had a literal interpretation of the rule which is now being recommended to the Board of Regents."

DR. WRIGHT: "I second the amendment to the motion."

ADMIRAL JOEL T. BOONE: "The term Armed Forces has been used, and we would like to extend the possibility of that to the 'Veterans Administration,' because those people are subject to orders. I probably can speak, too, for 'Public Health.' All serve the same situation."

CHAIRMAN DOAN: "Of course, the records would be perfectly available there."

DR. J. MURRAY KINSMAN: "I, too, object to setting any time limit in the By-Laws, because, having served on the Credentials Committee, it is obvious that there are many times when it has been very important there should not be a rigid restriction in number of years of residence. For Fellows it is different. I am entirely in sympathy with Dr. Wakefield's expression, namely, that we should not here today decide on a final course of action in regard to this matter, but should talk with the Regents further."

DR. MCCARTHY: "That is already taken care of. The motion provides exceptions, because it gives the Board of Regents discretionary powers under exceptional conditions."

CHAIRMAN DOAN: "The motion is that there be a change by the transmission of the applicability of the three-year minimum residence period for Fellowship to Associateship, as a recommendation to the Board of Regents, with the discretionary powers given in the case of Fellowship also given in the case of Associateship.

"The amendment to the motion provides that in the case of candidates on duty with the Armed Services, Veterans Administration or the United States Public Health Service, or in institutions of acceptable training, may submit detailed records and analyses of their work and assignments and may be considered at the discretion of the Credentials Committee for a lesser term of residence than three years, that certification from those who have known the candidates in their previous periods of training be also considered by the Credentials Committee."

DR. DOUGLAS DONALD: "Is this three years, or should it be two years?"

CHAIRMAN DOAN: "It is three years. Dr. McCarthy finally directed that the same regulation be applied to Associateship as for Fellowship."

DR. LARSEN: "Mr. Chairman, I move the motion be tabled until next year."

DR. CHESTER S. KEEFER: "I second the motion."

. . . The motion was put to vote and passed. . . .

CHAIRMAN DOAN: "Dr. Larsen, have you a matter that you would like to bring up before this Board?"

DR. LARSEN: "In Honolulu we had an Associate of the College, but who could not qualify for Fellowship because he was not eligible to become a citizen. There is an unusual situation in Hawaii. There have been at different times three large migrations. When these migratory groups came they brought children. This par-

ticular Associate of the College, to whom I refer, was about six months old when his family came to Hawaii. He is primarily Japanese. Many of these are excellent men, trained in our best American universities, and they take an active part in the community, but they are not eligible to citizenship under the present rules of our country. As far as the American College is concerned and its local group in Hawaii, we would like to have an opinion from the Governors on our wish to pass favorably on a few of these men in the category of the Japanese member I spoke of for admission to the College. It is unfair in their particular case—they would like to be American citizens, but are excluded because of discriminatory laws governing citizenship."

SECRETARY LOVELAND: "It has been the policy of the American College of Physicians to accept for consideration for membership only citizens of some North American country, or its territories. In Hawaii there are a number of physicians who actually, because of their race, though they may be fully acceptable professionally and personally, cannot qualify for citizenship and, therefore, are not eligible for membership in the College.

"We have many inquiries concerning membership in the College from physicians in Europe, in India and other parts of the world, and we promptly inform them that they are not eligible, unless they are citizens of a North American country. There is a distinct difference, however, between those cases and those to which Dr. Larsen refers in Hawaii."

DR. MCGEE: "The Credentials Committee is merely carrying out the dictates of the Board of Governors and the Board of Regents in this matter. This recommendation of Dr. Larsen would be quite acceptable to the Credentials Committee if the Board of Governors and the Board of Regents were to make any waiver of the citizenship requirement. Most of us recognize citizenship is a requirement basic to almost any medical society membership and quite essential to licensing. For some years we have been accepting all sexes, races and colors. We have shown no discrimination."

DR. LARSEN: "These men can be licensed in Hawaii. They are members of the local medical society, and to all intents and purposes are citizens, but not legally so. They are members of the American Medical Association."

CHAIRMAN DOAN: "The sentiment of this body is that the Board of Regents look into that problem as a special consideration."

. . . It was moved and seconded that Chairman Doan's suggestion be carried out. . . .

CAPTAIN ROBERT A. BELL: "It is my understanding that if those gentlemen are citizens of the Territory of Hawaii, they are citizens of the United States, and I am wondering if this particular doctor, having come to Hawaii at a tender age, why he has never become a citizen of Hawaii?"

DR. LARSEN: "As I understand it, you cannot become a citizen of an integral part of the United States without becoming a citizen of the United States, and you are not allowed to become a citizen of the United States if you were born in certain countries—no matter how long you are in residence."

DR. BRISCOE: "We have a situation similar in Panama. Some doctors are not citizens and yet we recognize them as a part of this organization."

DR. LARSEN: "Mr. Chairman, I do want to make the comment that we hope within a very short time that we will be the 49th State. However, that wouldn't change the status, as far as the rule is concerned."

DR. WALTON: "In Canada we have this sort of a situation—not on racial grounds, but because the Canadian Citizenship Act has only been in force for some four or five years. Prior to that a British citizen was a resident of Canada. Now a British citizen has to be a resident of Canada for some years before he can take out our formal citizenship. That means that within the last four or five years I have had much

correspondence with Mr. Loveland's office concerning young doctors, qualified men, who cannot be called Canadian citizens for some years to come."

CHAIRMAN DOAN: "Then, we shall include the Canadian situation along with the Hawaii problem in our motion."

. . . The motion was put to vote and carried. . . .

DR. T. GRIER MILLER: "May I take this opportunity of expressing my appreciation for being allowed to attend this meeting? Unfortunately, I have never been a Governor of the College, and now that I have many heavy responsibilities on my shoulders, I feel that had I been a Governor, I would be in a much better position to perform my duties.

"I have been very much interested in all of the discussions that have taken place here today, and I am particularly pleased that the motion was passed not to require certification for Associateship. I appreciate the fact that the American Board of Internal Medicine was first initiated by our College, and I certainly think that most of the men who come into Fellowship should have passed that Board. At the same time, I think we should continue to leave a loophole, because there are certain men coming up in the fundamental sciences and then getting into clinical medicine, interested in one particular phase of medicine, men who are never going to take the Board examination, but who ought to be in this College.

"In support of that, I would like to say that an analysis of the programs of the Annual Sessions of this College for the past four years discloses that 40% of the speakers are not Fellows of the College. Now, those are men that we want in this College, and yet we are going outside to get them."

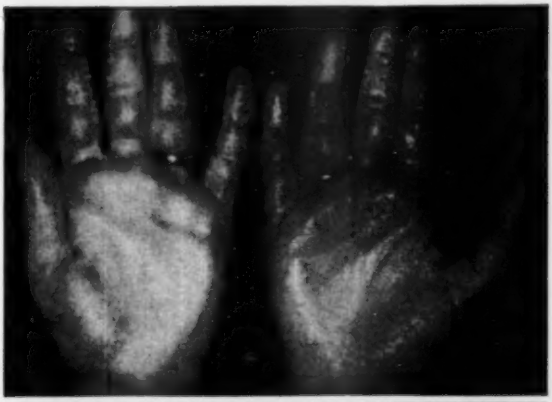
CHAIRMAN DOAN: "Thank you, Dr. Miller. I am sure we in the Board of Governors pledge you every support in your administration next year. If there is any service we can perform, please let us know, individually or collectively."

. . . The business of the day being concluded, the meeting adjourned at 2:30 o'clock. . . .

Adjournment.

Attest: E. R. LOVELAND,
Secretary

Excessive Perspiration



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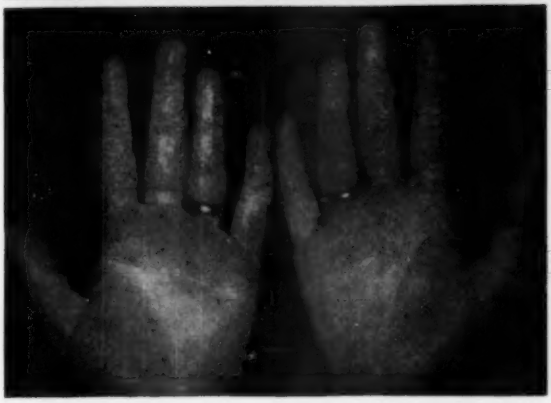

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